Dopaminylation in Psychostimulant Use Disorder Protects Against Psychostimulant Seeking Behavior by Normalizing Nucleus Accumbens (NAc) Dopamine Expression

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Abstract

Background: Repeated cocaine administration changes histone acetylation and methylation on Lys residues and Deoxyribonucleic acid (DNA) within the nucleus accumbens (NAc). Recently Nestler's group explored histone Arg (R) methylation in reward processing models. Damez-Werno *et al.* (2016) reported that during human investigations and animal self-

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administration experiments, the histone mark protein-R-methyltransferase-6 (PRMT6) and asymmetric dimethylation of R2 on histone H3 (H3R2me2a) decreased in the rodent and cocaine-dependent human NAc. Overexpression of PRMT6 in D2-MSNs in all NAc neurons increased cocaine seeking, whereas PRMT6 overexpression in D1-MSNs protects against cocaine-seeking.

Hypothesis: The hypothesis is that dopaminylation (H3R2me2a binding) occurs in psychostimulant use disorder (PSU), and the binding inhibitor Srcin1, like the major DRD2 A2 allelic polymorphism, protects against psychostimulant seeking behavior by normalizing nucleus accumbens (NAc) dopamine expression.

Discussion: Numerous publications confirmed the association between the DRD2 *Taq A1* allele (30–40 lower D2 receptor numbers) and severe cocaine dependence. Lepack *et al.* (2020) found that acute cocaine increases dopamine in NAc synapses, and results in histone H3 glutamine 5 dopaminylation (H3Q5dop) and consequent inhibition of D2 expression. The inhibition increases with chronic cocaine use and accompanies cocaine withdrawal. They also found that the Src kinase signaling inhibitor 1 (Srcin1 or p140CAP) during cocaine withdrawal reduced H3R2me2a binding. Consequently, this inhibited dopaminylation induced a "homeostatic brake."

Conclusion: The decrease in Src signaling in NAc D2-MSNs, (like the DRD2 Taq A2 allele, a well-known genetic mechanism protective against SUD) normalizes the NAc dopamine expression and decreases cocaine reward and motivation to self-administer cocaine. The Srcin1 may be an important therapeutic target.

Keywords

Src; p140CAP; psychostimulants; cocaine; histone arginine (R) methylation; medium spiny neurons; DRD2 gene

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1. INTRODUCTION

In 2013 Blum's group asked the question related to why people drink alcohol or get involved in high rates of drug-seeking behaviors. Other compelling questions surround the millions who seek out high-risk novelty situations are as follows: "Why are millions paying the price of their indiscretions in our jails, in hospitals, in wheelchairs, and are lying dead in our cemeteries. What price must we pay for pleasure-seeking or just plain getting "HIGH"? Maybe the answer lies within our brain. Maybe it is in our genome" [1].

In 2020, Americans faced the worst opioid epidemic, with as many as 185 people dying daily from opioid-related events [2]. There is robust evidence that cognitive, emotional, and behavioral disturbances observed in psychiatric illnesses, including Reward Deficiency Syndrome (RDS), connect with functional deficits in neurological networks [3–8].

Blum *et al.* identified Reward Deficiency Syndrome (RDS) in 1995 as a putative predictor of impulsive and addictive behaviors [9–12]. Many behavioral phenotypes, including neuropsychiatric disorders, aggression [13], alcoholism, and other rewarding and addictive behaviors [14], are associated with the DRD2 TaqI A1 allele. The DRD1 and DRD2 genes are both involved in reward mechanisms [15]. The net effect of biochemical actions in mesolimbic structures leads to rewarding phenomena when dopamine (DA) levels increase

in synaptic spaces; within the nucleus accumbens, where DA interacts with DRD1 and DRD2 and other subtypes of receptors [16, 17]. Positron emission tomography (PET) studies have reported lower DRD2 availability in psychostimulant and alcohol-dependent and obese individuals than control participants [18–20].

Importantly, Noble, Blum, and colleagues [21] had also observed that the A1 and B1 minor alleles of the gene were associated with cocaine use disorder (CUD). These findings suggest that the DRD2 gene, located on q22-q23 region of chromosome 11, conferred susceptibility to psychostimulant use disorder (PUD). These results agreed with Gold's group's early reports that had suggested that the D2 agonist, bromocriptine, might have therapeutic potential against cocaine abuse and dependence [22]. However, unlike the DRD2 *Taq A1* allele with a reduced number of D2 receptors, the DRD2 *Taq A2* allele, the major variant, has a normal complement of D2 receptors that could be protective against psychostimulant abuse.

1.1. Hypothesis

Hypothesizing that dopaminylation H3R2me2a binding) occurs in CUD and during withdrawal, inhibitor Srcin1 or p140Cap blocks H3R2me2a binding and normalizes dopamine expression at the Nucleus Accumbens (NAc) like the major DRD2 Taq A2 allelic polymorphism, and both mechanisms are protective against psychostimulant seeking behavior.

2. UNDERSTANDING THE ROLE OF PROTEIN R METHYLTRANSFERASE (PRMT) PSYCHOSTIMU-LANT ABUSE

Cocaine increases dopamine neurotransmission from the ventral tegmental area (VTA) to reward-relevant brain regions. This well-known cocaine action is central to its addictive properties. Recently a role for serotonin (5-HT) in developing 5-HTergic neurons has been described whereby 5-HT located in the nucleus of these neurons covalently attached to histone proteins—specifically on H3 (H3Q5)—to regulate gene expression through a called serotonylation [23]. This mechanism has been generalized to other brain monoamines, such as dopamine. paminylation is a process in which a transglutaminase 2 protein can directly attach dopamine molecules to histone proteins [24]. The process of dopaminylation (H3Q5dop) and its role in cocaine abuse is the primary subject of this review and hypothesis.

Repeated exposure to cocaine regulates transcriptional events within the nucleus accumbens (NAc) *via* epigenetic mechanisms, that change the expression of the individual's Deoxyribonucleic Acid (DNA) according to individual genetics [25]. Changes in epigenetic markers that include histone acetylation and methylation on Lys (K) residues, as well as DNA methylation, accompany the use of psychostimulants such as cocaine and methamphetamine [26]. Specifically, methamphetamine use disorder (MAUD) is a biopsychosocial disorder accompanied by multiple relapses even after prolonged abstinence. These multiple relapses are attributed to the long-lasting, maladaptive epigenetic changesin the brain.

Cadet's group has used multiple biochemical and molecular approaches, including chromatin immunoprecipitation (ChIP) And quantitative PCR assays to demonstrate epigenetic changes in the NAc -rat and dorsal striatum of rats exposed to methamphetamine [27]. For example, methamphetamine increased the amount of phosphorylated (pCREB) bound at the promoter of several genes related to drug-seeking behaviors. Methamphetamine also initiated DNA hypomethylation at sites near the Crh transcription start site (TSS) and intragenic Avp sequences and DNA hydroxymethylation at the Crh TSS and intragenic Avp sites. Itis further noteworthy that methamphetamine increased the protein expression of ten-eleven-translocation enzymes that catalyze DNA hydroxymethylation. Methamphetamine increased TET1 binding at the Crh promoter and increased TET3 binding at Avp intragenic regions. Cadet's group has also shown that chronic methamphetamine self-administration can result in DNA hydroxymethylation of potassium channels in the nucleus accumbens [28] necessary for regulating DA release.

Reports in the literature also demonstrated the functional role of histone Arg (R) methylation [28] in contrast to lysine(K) methylation. The methylation of R residues catalyzed by the protein R methyltransferase (PRMT) enzymes generates methylated R states with differentially diverse functional consequences, including monomethyl arginine (MMA) and dimethylarginine (DMA) residues [29]. In chromatin architecture, alterations are induced by R methylation; they either relax or condense its structure to create binding sites for regulatory proteins that contain specialized binding domains. These histone tails are targets for PRMTs and can affect gene expression [30, 31].

Frankel *et al.* [32] suggest that PRMT6 in mammalian cells may controlasymmetric dimethylation of R2 on histone H3 (H3R2me2a). Further, others have shown that H3R2me2a 5 mark may be repressive in nature due to its ability to counter the activation function of the nearby H3K4me3 mark [33]. Interestingly, Feng *et al.* [34] previously demonstrated an enrichment of the H3K4me3 mark that was pronounced at focal gene promoters in the rodent NAc after repeated cocaine exposure. Similarly, Kennedy *et al.* [35] showed that Class I HDAC inhibition blocks duced plasticity by targeted changes in histone methylation, providing more acetyl groups, and induced repressive histone methylation antagonizing cocaine-induced behaviors. Mostly, this effect *via* a chromatin-mediated suppression of GABA$_A$ receptor subunit expression results in an inhibitory tone on NAc neurons in the ventral tegmental area (VTA) and will increase dopamine release into the synapse. Indeed, this chromatin-mediated suppression of GABA$_A$ receptor subunit expression disinhibits the GABA$_A$ break on NAc dopamine release to overcome the chronic cocaine-induced loss of dopamine function [36].

Further, the proposition is that long-term cocaine abuse is due to its remarkable inhibition of presynaptic dopamine transporters that prevent the reabsorption of dopamine required for the next action potential and subsequently further decreases new dopamine synthesis. This lack of dopamine transported from the mitochondria (not the synaptic cleft) to the pre-neuronal dopamine storage vesicles compromises the enzyme tyrosine hydroxylase (rate-limiting for pamine synthesis) required to catalyze more synthesis of dopamine to overcome a "homeostatic break" [37]. Specifically, Trulson *et al.* [37] found that chronic administration of cocaine (for10 consecutive days of 10 mg/kg, IP, every 12 hours) generally decreased

tyrosine hydroxylase staining of axons and terminal boutons in the rat frontal cortex and NAc terminals, which originate from the midbrain VTA. treatment also produced a long-lasting depletion of tyrosine hydroxylase immunoreactivity in the VTA when examined 60 days following the final cocaine injection. The authors concluded that: *"these data demonstrated that chronic administration of cocaine produces a long-term, if not permanent, loss of tyrosine hydroxylase enzyme in both the bodies of the midbrain ventral tegmental area as well as in the nerve terminals in post-synaptic target regions of forebrain."*

Damez-Werno *et al.* [29] were the first to report that after repeated cocaine exposure, PRMT6 and its associated histone mark, asymmetric dimethylation of R2 on histone H3 (H3R2me2a), decreased in the NAc of mice and rats as well as in the NAc of cocaine-addicted humans. PRMTs regulate multiple biological processes that include DNA transcription, mRNA splicing, and piRNA biogenesis; however, little is known about the regulation of *Prmt* translation from mRNA into protein. Specifically, they revealed that cocaine-induced PRMT6 down-regulation occurs selectively in NAc medium spiny neurons expressing dopamine D2 receptors (D2-MSNs) and serves to protect against cocaine-induced behavioral abnormalities like anhedonia. Moreover, cocaine-induced PRMT6 up-regulation occurs selectively in NAc medium spiny neurons expressing dopamine D1 receptors (D1-MSNs). Therefore, the function of PRMT6 is consistent with opposing the activation of D2 and D1 receptor containing neurons in the NAc to dampen the final output from the ventral striatum. This group also found that Src kinase signaling inhibitor 1 (Srcin1 or p140Cap) is a key target for this chromatin modification. Srcin1 induction in the NAc after cocaine exposure, which is associated with reduced Src signaling, decreases cocaine reward and self-administration. To induce homeostatic feedback and prevent cocaine-induced abnormalities, one would expect a requirement that enables the normal expression of both D1 and D2-MSNs. However, albeit currently unexplained, the regulatory role of PRMT6 as induced by long-term cocaine abuse seems to selectively down-regulate D2-MSNs relative to D1-MSNs.

2.1. To Be Or Not Be D2

Dopamine is the neurotransmitter involved in motivation and reward behavior. When dopamine is chemically attached to histone proteins, cells switch different genes on and off to significantly affect cocaine vulnerability and relapse. Damez-Werno *et al.*, as stated, persuasively demonstrated the downregulation of PRMT6 in the NAc of mice and rats treated repeatedly with cocaine. They also demonstrated this effect in cocaine-addicted postmortem humans. Cocaine down-regulation of PRMT6 seems to be specific toD2 MSNs in this brain region. Accordingly, Nestler's group also suggested that this effect constitutes a homeostatic response and reinforces the hypothesis that this D2 MSN subtype is necessary to mediate and oppose cocaine-addictive behavior [29]. Elucidation of the role of PRMT6 in the NAc revealed that cocaine-induced decreases in H3R2me2a and increases in H3K4me3. Specifically, with chronic cocaine, there is an induction of the inhibitory gene*Srcin1*. Coincidental, with the induction of the*Srcin1* by cocaine, is the suppression of the Src signaling pathway. Such resultant suppression mimics the similar suppression as observed with PRMT6/H3R2me2a along with subsequent opposition to the rewarding effects of cocaine, including self-administration of the drug. Previous work had

demonstrated that H3R2 methylation by PRMT6 is prevented by H3K4me3, confirming H3R2me2a's transcriptional repressive role [32]. From the neuro-psychopharmacological viewpoint, D1-MSNs *vs.* D2-MSNs have opposite roles in drug addiction. D1-MSNs promote both reward and sensitizing responses to psychostimulants, while D2-MSNs dampens these behaviors [37]. Thus, after cocaine exposure, increased PRMT6 levels in D1-MSNs and decreased PRMT6 levels in D2-MSNs may form a homeostatic response toward a common outcome, both opposing cocaine-addictive behaviors. In support of this hypothesis, *Srcin1* overexpression in the NAc exerts anti-addictive properties by opposing the rewarding responses to cocaine. What is even more remarkable, this action of *Srcin1* (**p140Cap**), like that of PRMT6, appears to be specific to D2-MSNs.

These findings indicate a novel role of histone R methylation as a key regulator in the induction of *Srcin1*, an Src signaling repressor that opposes cocaine action. This work further suggests, in particular, the importance of D2 –MSNs in anti-cocaine effects [21] and provides additional supporting evidence to tag DRD2 function as a therapeutic target for the treatment of cocaine addiction. These findings relate to the possibility that vulnerability to relapse during periods of attempted cocaine abstinence results from the rewiring of brain reward circuitries, particularly VTA dopamine neurons such as D2 receptors [38]. In terms of relapse, especially in Alcohol Use Disorder (AUD), reduced dopamine D2 receptor (D2R) ligand binding has repeatedly been demonstrated in the human striatum. The attenuated D2R binding reflects reduced D2R density [18], which drives craving and relapse.

Moreover, long-term voluntary alcohol drinking significantly reduced mRNA levels of the long D2R isoform in the NAc [24]. Notably, alcohol intake reduced the striatal density of D2R-D2R homoreceptor complexes and increased the density of NAc shell A2AR (adenosine) -D2R heteroreceptor complexes, and decreased the density of sigma1R-D2R heteroreceptor complexes in the dorsal striatum. Understandably, Feltmann *et al.* [39] suggested that both reduced striatal D2R levels and reduced D2R protomer affinity within the striatal A2AR-D2R complex might underlie reduced D2R radioligand binding in humans with AUD. These intriguing results support the Blum group [40] hypothesis of a hypodopaminergic system in AUD and propose that the D2R heteroreceptor complex is a potential novel treatment target. With that stated, there is strong evidence that DRD2 A1 allele may induce relapse to not only alcoholism [41] but cocaine [42]. As previously stated, distinct populations of D1-and D2-dopamine receptor-expressing medium spiny neurons (D1-/D2-MSNs) comprise the nucleus accumbens, and activity in D1-MSNs promotes, whereas activity in D2-MSNs inhibits motivated behaviors. Heinsbroek *et al.* [42] demonstrated that both cell types sent GABAergic projections to the ventral pallidum and promoted cue-induced reinstatement of cocaine-seeking *via* the ventral pallidum differentially. After cocaine self-administration, selectively D2, but not D1, lose synaptic plasticity to the ventral pallidum's inputs. The selective impairment in D2 afferents may promote D1 inputs' influence to drive relapse to cocaine seeking.

Lepack *et al.* [24] also found a critical role in cocaine-induced transcriptional plasticity for the midbrain Transglutaminase a protein, directly attaches dopamine molecules to histone proteins. This process histone paminylation or H3Q5dop occurred during periods of caine withdrawal when rodents showed an accumulation of H3Q5dop in the VTA. Lepack *et al.*

reduced cocaine-seeking behavior, attenuated dopamine release in the nucleus accumbens, and reversed cocaine-mediated gene expression changes by reducing H3Q5dop in the VTA during cocaine withdrawal (see Fig. 1). As stated earlier, while the relatively new concept of histone and the formidable work by Jayanthi *et al.* from NIDA [27] concerning Methamphetamine induced TET1- and TET3-Dependent DNA hydroxymethylation of Crh and Avp Genes in the rat NAc may suggest a generalized molecular epigenetic DNA hydroxymethylation and subsequent regulation at possibly the transcriptional 3' loci as first found by Blum *et al.* [43], concerning the polymorphisms in the DRD2 gene.

Finally, the demonstration by Lepack *et al.* [24] regarding their seminal finding that Src kinase signaling inhibitor 1 (p140CAP) during cocaine withdrawal reduced H3R2me2a binding was indeed a protective mechanism in downregulating PRMT6 in the NAc. Consequently, inhibited dopaminylation induced a "homeostatic brake," with a decrease NAc D2-MSNs Src signaling and subsequently reduced cocaine reward and motivation to self-administer cocaine. These findings mimic earlier publications from Blum and Noble's group [18, 21, 43] in terms of not only cocaine but alcoholism, and Volkow's group [44] on ADHD, that suggested that DRD2 Taq A2 allele is an inborn protective mechanism.

Recently a study by the Gondré-Lewis group45 [] at Howard University utilized a known model for binge drinking found that alcohol-preferring (P) adult male and female rats significantly mitigated their alcohol intake when treated with a neuro-nutrient, KB220Z, designed to augment DA signaling. Surprisingly, preliminary studies of KB220Z initially found fewer DRD2 punctae in neurons of the NAc. However, corrected for volume and cell number, the NAc shell expressed more DRD2 mRNA per cell than the NAc core. Independent of KB220Z, the study indicated a non-significant trend where KB220Z induced down-regulation of DRD2 mRNA in D2-MSNs.While expected, KB220Z up-regulation of the D2-MSNs, the importance of down-regulation of PRMT6 specific to D2-MSNs now understood to combat drug addiction, future research in our laboratory will attemptto dissect this exciting potential (see Fig. 2).

In terms of psychostimulant induced alterations in brain structure and function, including microglia, a series of experiments involving methamphetamine should also be considered beyond DNA methylation and subsequent regulation of gene expression [46–49].

CONCLUSION

In conclusion, the histone-DNA spool to enable environmentally environmentally regulated alterations in gene expression. Due to this functional rewiring of the VTA reward circuitry, histone dopaminylation drives heightened vulnerability in chronic CUD. The buildup of H3Q5dop in the VTA can increase cocaine-seeking behavior. In contrast, reducing H3Q5dop in rats undergoing cocaine withdrawal significantly reversed gene expression changes and reduced caine-seeking behavior [24]. These findings also clearly establish a neurotransmission-independent role for neuronal dopamine in relapse-related transcriptional plasticity in the VTA [24]. Thus, histone arginine dopaminylation occurs in psychostimulant abuse, and the H3R2me2a binding inhibitor Srcin1 or p140Cap normalizes dopamine

expression at the NAc, which mimics DRD2 A2 allelic polymorphic protection against psychostimulant seeking behavior.

Understanding these complex neurogenetic and novel epigenetic mechanisms concerning psychostimulant and alcohol use disorders, we continue to promote the need for DA homeostasis in addiction treatment and prevention. These activities will require studies using genetic addiction risk assessment with a nutrigenomic precision behavioral management that occasionally seeks epigenetic repair, encouraging dopamine homeostasis to prevent drug and non-drug seeking behaviors [42].

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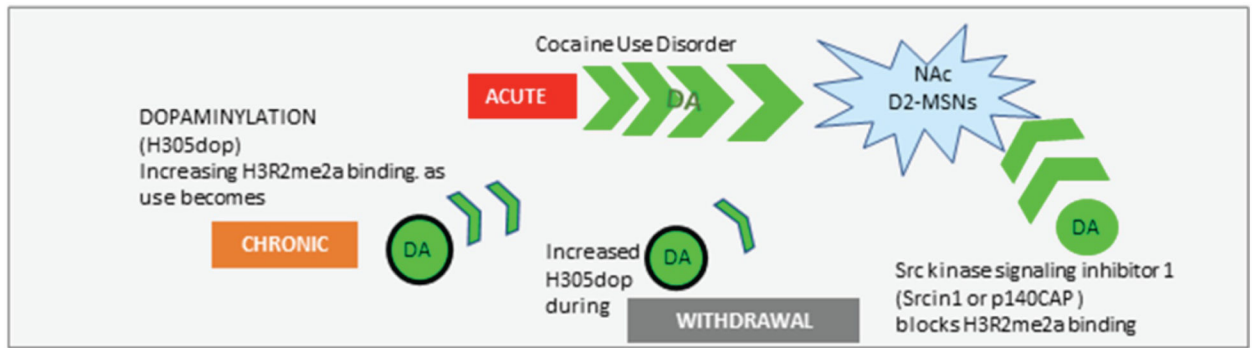
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Fig. (1). Dopaminylation in Cocaine Use and Withdrawal.
Illustrates how histone arginine dopaminylation that occurs in psychostimulant abuse is combated by H3R2me2a binding inhibitor Srcin1 and during withdrawal and normalizes dopamine expression at the Nucleus Accumbens (NAc) and like the major DRD2 A2 allelic polymorphism is protective against psychostimulant seeking behavior. DA = Dopamine.
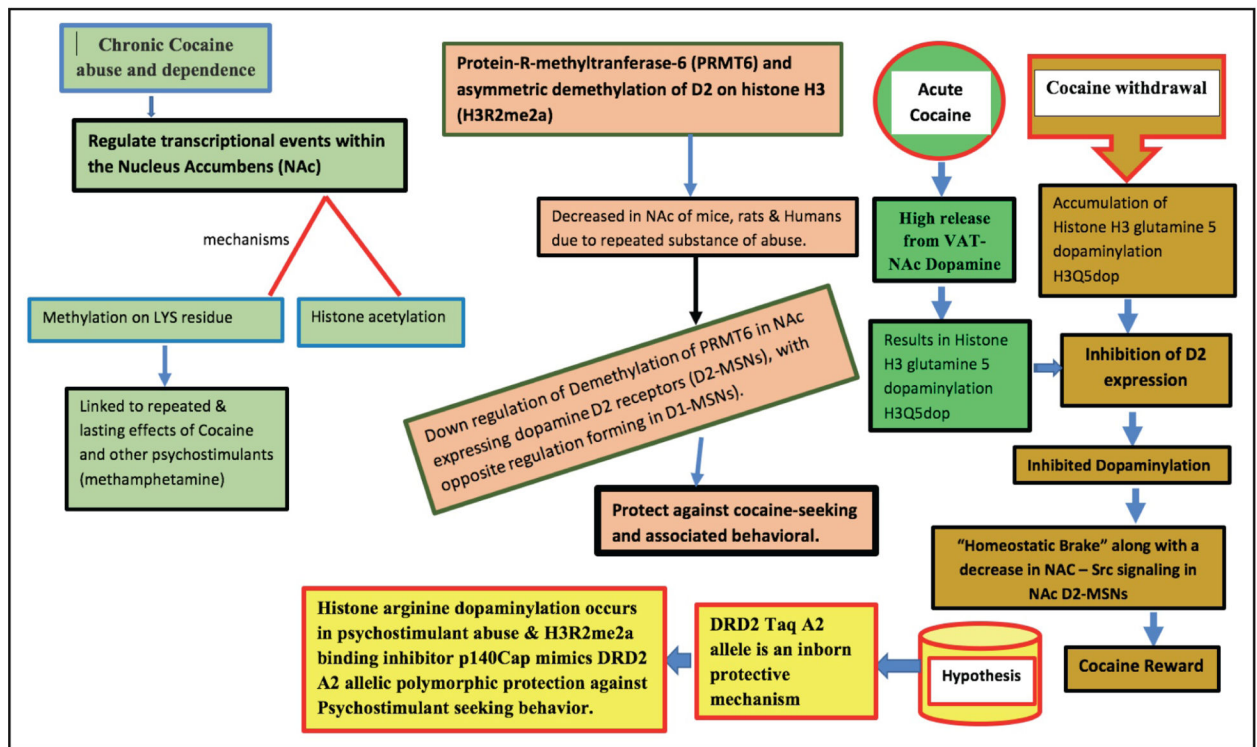
Fig. (2). Epigenetic and transcriptional effects of chronic cocaine exposure and psychostimulant abuse.

Histone acetylation and methylation on Lys residues result from cocaine and methamphetamine abuse (dull green). After repeated cocaine exposure, Protein-arginine (R)-methyltransferase-6 (PRMT6) and its associated histone decreased in the NAc of mice and rats and the NAc of cocaine-dependent humans due to dimethylation of R2 on histone H3 (H3R2me2a), which was asymmetric. Downregulation of demethylation by PRMT6 selectively occurred in NAc medium spiny neurons (MSNs) expressing dopamine D2 receptors (DRD2) (D2-MSNs), with opposite regulation manifested in D1-MSNs. These changes appeared to protect against cocaine-seeking and associated behavioral abnormalities (dull orange). Acute cocaine increased DA and histone H3 glutamine 5 dopaminylation (H3Q5dop), with a secondary decreased in D2 expression (bright green). Withdrawal from cocaine led to the accumulation of histone H3 glutamine 5 dopaminylation (H3Q5-dop) and subsequent D2 expression inhibition. Administration of the Src kinase signaling inhibitor 1 (p140CAP) during cocaine withdrawal reduced H3R2me2a binding. Inhibited dopaminylation induced a "homeostatic brake" and decreased NAc Src signaling in NAc D2-MSNs accompanied by decreased cocaine reward and motivation to self-administer cocaine (tan). These results are consistent with the idea that the DRD2 Taq A2 allele serves as a genetic protective mechanism (bright yellow).