HHS Public Access

Author manuscript

Neuroscience. Author manuscript; available in PMC 2018 June 14.

Published in final edited form as:

Neuroscience. 2017 June 14; 353: 1–6. doi:10.1016/j.neuroscience.2017.04.007.

Regulation of BAZ1A and Nucleosome Positioning in the Nucleus Accumbens in Response to Cocaine

HaoSheng Sun[1], **Diane M. Damez–Werno**[1], **Kimberly N. Scobie**[1], **Ning–Yi Shao**[1], **Caroline Dias**[1], **Jacqui Rabkin**[1], **Katherine N. Wright**[2], **Ezekiell Mouzon**[1], **Mohamed Kabbaj**[2], **Rachael Neve**[3], **Gustavo Turecki**[4], **Li Shen**[1], and **Eric J. Nestler**[1,*]

[1]Fishberg Department of Neuroscience and Friedman Brain Institute, Icahn School of Medicine at Mount Sinai, New York, NY, USA 10029

[2]Department of Biomedical Sciences, Florida State University, Tallahassee, FL, USA 32306

[3]Department of Brain and Cognitive Sciences, Massachusetts Institute of Technology, Cambridge, MA, USA 02139

[4]McGill University, Montreal, Canada

Abstract

Chromatin regulation, in particular ATP-dependent chromatin remodelers, have previously been shown to be important in the regulation of reward-related behaviors in animal models of mental illnesses. Here we demonstrate that BAZ1A, an accessory subunit of the ISWI family of chromatin remodeling complexes, is downregulated in the nucleus accumbens (NAc) of mice exposed repeatedly to cocaine and of cocaine-addicted humans. Viral-mediated overexpression of BAZ1A in mouse NAc reduces cocaine reward as assessed by CPP, but increases cocaine-induced locomotor activation. Furthermore, we investigate nucleosome repositioning genome-wide by conducting ChIP-sequencing for total H3 in NAc of control mice and after repeated cocaine administration, and find extensive nucleosome occupancy and shift changes across the genome in response to cocaine exposure. These findings implicate BAZ1A in molecular and behavioral plasticity to cocaine and offer new insight into the pathophysiology of cocaine addiction.

Keywords

cocaine; addiction; epigenetics; chromatin; chromatin remodeling

Introduction

Chromatin regulation—in particular histone writers and erasers as well as proteins that control DNA methylation—is important for mediating the effects of repeated cocaine

*Correspondence: Eric J. Nestler, eric.nestler@mssm.edu.

exposure on nucleus accumbens (NAc) gene expression and cocaine reward-related behaviors (Renthal et al., 2007, LaPlant et al., 2010, Maze et al., 2010, Covington et al., 2011, Malvaez et al., 2013, Rogge et al., 2013, Deng et al., 2014, Feng et al., 2015, Sartor et al., 2015, Wright et al., 2015, Damez-Werno et al., 2016). ATP–dependent chromatin remodelers also play an important role in regulating gene expression by altering nucleosome positioning, and have been implicated in modulating learning and memory behaviors as well as regulating reward-related behaviors in animal models of depression and drug addiction (Whitehouse et al., 2007, Clapier and Cairns, 2009, Yen et al., 2012, Narlikar et al., 2013, Vogel-Ciernia et al., 2013, Sun et al., 2015, Sun et al., 2016). Specifically, the persistent induction of BAZ1A, an accessory subunit of the ISWI family of chromatin remodeling proteins, has been shown to be important in mediating repeated stress-induced depressive-like behaviors through nucleosome repositioning in NAc (Sun et al., 2015). Here, we characterize the regulation of BAZ1A and nucleosome positioning in NAc after repeated cocaine exposure.

Experimental Procedures

Animals

C57BL/6J male mice (7–8 weeks old; Jackson Laboratory, Bar Harbor, ME USA) were housed at constant temperature (23°C) on a 12 hours light/dark cycle with *ad libitum* access to food and water. All protocols were approved by Mount Sinai's IACUC unless specified otherwise.

Human postmortem brain tissue

Human NAc brain tissue was obtained from the Quebec Suicide Brain Bank (QSBB; Douglas Mental Health Institute, Verdun, Québec). All individuals were group–matched for age, pH, and postmortem intervals (PMI). Inclusion criteria for both cocaine-addicted individuals and controls were the following: the subject had to be Caucasian and of French Canadian origin, and die suddenly without prolonged agonal state. NAc was stored at −80°C. This study was approved by the Douglas IRB and signed informed consent was obtained from next of kin.

Cocaine administration

Cocaine hydrochloride (Sigma-Aldrich, St. Louis, MO USA) was dissolved in sterile 0.9% saline (wt/vol). Daily i.p. saline or cocaine (20 mg/kg) injections were administered in the animals' home cages.

NAc RNA isolation and qRT–PCR

Total RNA was isolated from the NAc of individual mice and qRT-PCR was performed as described previously (Sun et al., 2015, Sun et al., 2016). Briefly, bilateral 14 gauge punches of NAc were obtained at varying times after the last cocaine or saline injection and frozen on dry ice until further use. Samples were homogenized in TRIzol, purified with RNAeasy Micro columns, reverse transcribed using an iScript Kit, and quantified using SYBR green. Each reaction was performed in duplicate and normalized to glyceraldehyde–3–phosphate dehydrogenase (*Gapdh*) levels, which were not themselves altered by cocaine exposure.

Western blotting

Western blotting was performed as described previously (Sun et al., 2015, Sun et al., 2016). Briefly, frozen bilateral NAc punches from individual mice were homogenized in RIPA buffer, and 50 μg of protein were loaded onto 4–15% gradient Tris–HCl polyacrylamide gels for electrophoresis (Bio–Rad). Proteins were transferred to nitrocellulose membranes, which were then blocked with Odyssey® blocking buffer (Li–Cor, NE, USA), and incubated overnight at 4°C with primary antibodies (BAZ1A: Bethyl A301–318A) in Odyssey® blocking buffer. The next day, membranes were incubated with IRDye® secondary antibodies (1/5000; Li–Cor, Lincoln, NE, USA; 1 hour at room temperature) in between washes with 1× Tris–Buffered Saline plus 0.1% Tween–20. Blots were imaged with the Odyssey® Infrared Imaging system (Li–Cor, Lincoln, NE, USA) and quantified by densitometry using ImageJ (NIH, Bethesda, Maryland, USA). The amount of protein blotted onto each lane was normalized to levels of GAPDH or β-tubulin, neither of which was altered in NAc by cocaine exposure.

Viral–mediated gene transfer—Viral-mediated gene transfer was performed as described previously (Sun et al., 2015, Sun et al., 2016). Briefly, mice were positioned in stereotaxic instruments under ketamine (100 mg/kg)/xylazine (10 mg/kg) anesthesia and thirty–three gauge syringe needles were bilaterally lowered into NAc (anterior/posterior + 1.6; medial/lateral + 1.5; dorsal/ventral − 4.4 mm from Bregma, 10° angle) to infuse 0.5 μl of HSV-GFP or HSV-BAZ1A.

Conditioned place preference (CPP)—CPP was performed as described previously beginning one day after viral surgery (Sun et al., 2016). Briefly, animals were trained in a three-chamber apparatus with two distinct side chambers. After a baseline preference measure, which showed that mice exhibit no pre-existing bias for either side chamber, mice were conditioned for 30 minutes over 2 days to the saline-paired side in the morning and the cocaine-paired side (7.5 mg/kg i.p.) in the afternoon. On the final day, mice were placed again in the central compartment at noon and allowed to move freely between the two side chambers for 20 minutes. CPP scores were calculated as time spent in the cocaine-paired chamber minus time spent in the saline-paired chamber. This dose of cocaine was previously determined to reveal both increases and decreases in CPP after experimental manipulations.

Locomotor activity—For the 1st locomotor experiment, mice were injected with saline and habituated in a locomotor recording chamber for 30 minutes after recovery from stereotaxic surgery (Scobie et al., 2014, Sun et al., 2016). Then, for the next 5 days, locomotor activity was monitored for 30 minutes immediately after cocaine injections (10 mg/kg i.p.). For the challenge experiment, saline or cocaine (10 mg/kg i.p) was administered daily for 7 consecutive days, and animals were placed in the locomotor chamber and monitored for their activity. Following locomotor training, animals were given stereotaxic intra-NAc infusion of either HSV-GFP or -BAZ1A, allowed two days to recover, and then given a challenge injection of saline or cocaine (10 mg/kg i.p) and monitored for their locomotor activity for 30 minutes. This dose of cocaine was previously determined to reveal both increases and decreases in locomotor activity after experimental manipulations.

Chromatin immunoprecipitation (ChIP), library preparation, and sequencing— Published procedures were utilized (Feng et al., 2014, Sun et al., 2015). For each ChIP–sequencing (ChIP-seq) replicate, bilateral 14–gauge NAc punches were pooled from 5–10 mice, lightly fixed MNase digested, and immunoprecipitated using sheep anti–rabbit magnetic beads (Invitrogen) conjugated to an antibody targeting total H3 (Abcam). Immunoprecipitated DNA and total (input) genomic DNA were prepared for ChIP–seq using an Illumina kit according to the manufacturer's instructions. Each experimental condition was analyzed with independent biological triplicates.

ChIP–seq data analysis—ChIP–seq data alignment and analysis were conducted as described previously (Sun et al., 2015). ChIP-seq data were of sufficient quality and coverage for downstream nucleosome positioning determinations. For analysis of nucleosome position and occupancy, DANPOS was applied in the dynamic analysis of nucleosomes (Chen et al., 2013) with analysis parameters as described previously (Sun et al., 2015).

Statistical analysis—Student's t–tests were used whenever two groups were compared, while one–way and two–way ANOVAs were performed to determine significance for all other data. Significant main effects ($P < 0.05$) were further analyzed using post hoc tests.

Results

We first assessed the effect of i.p. cocaine administration on expression levels of *Baz1a* in mouse NAc (Fig. 1A). We found that *Baz1a* mRNA levels were transiently but significantly increased 1 hour after acute cocaine treatment (6 daily saline injections followed by a single 20 mg/kg cocaine injection on the 7th day) compared to saline controls (7 daily injections) (Fig. 1B left panel; t(33) = 2.814, $P = 0.008$). Levels returned to control levels 24 hours after cocaine injection (Fig. 1B right panel, 1D). In contrast, no change in *Baz1a* mRNA expression was observed 1 hour after repeated cocaine treatment (7 daily injections) compared to saline controls (Fig. 1B left panel; t(34) = 0.499, $P = 0.621$). Rather, there was a significant decrease in steady state BAZ1A mRNA and protein levels 24 hours after repeated cocaine administration (Fig. 1B right panel, 1D; mRNA: t(32) = 3.412, $P = 0.002$; protein: t(16) = 1.759, $P = 0.049$). *Baz1a* levels returned to saline control levels within 7 days after repeated cocaine administration (Fig. 1C). Decreased levels of BAZ1A protein was also observed in NAc of human cocaine-addicted individuals compared to controls (Fig. 1E; t(16) = 1.922, $P = 0.036$).

To directly examine whether altered BAZ1A levels in NAc are causally important in regulating cocaine reward behavior, we used HSV–mediated gene transfer to rapidly overexpress BAZ1A in this brain region (Sun et al., 2015). In an unbiased cocaine CPP paradigm, which provides an indirect measure of drug reward, animals with BAZ1A overexpression showed reduced cocaine preference (Fig. 2A; t(32) = 1.999, $P = 0.027$). Interestingly, BAZ1A overexpression in NAc increased locomotor responses to repeated cocaine exposures compared to HSV-GFP controls, while it did not affect locomotor behavior in response to saline injections (Fig. 2B, two-way ANOVA: group F(3,84) = 14.18, $P < 0.0001$; day F(5, 84) = 2.68, $P = 0.027$; interaction F(15,84) = 0.96, NS). Next, we

investigated whether BAZ1A overexpression in NAc affected locomotor behavior in response to a cocaine challenge after pre-treatment with saline or cocaine. Animals exhibited significantly greater locomotion after an acute cocaine challenge compared to a saline challenge with saline pre-treatment (Fig. 2C; first two bars: $t(9) = 4.346$, $P < 0.001$), and exhibited a further increase in locomotion after pre-treatment with cocaine (Fig. 2C; second and third bars: $t(11) = 1.999$, $P = 0.036$). Furthermore, BAZ1A overexpression in NAc enhanced still further locomotor responses to the cocaine challenge compared to HSV-GFP controls after cocaine pre-treatment (Fig. 2C; last two bars: $t(11) = 2.539$, $P = 0.014$). Together, these findings suggest that NAc BAZ1A is causally important in controlling behavioral responses to cocaine, but differentially regulates cocaine-induced reward vs locomotor activity.

Since BAZ1A-associated ISWI chromatin remodeling complexes regulate nucleosome repositioning (Whitehouse et al., 2007, Sala et al., 2011, Yen et al., 2012), we generated a nucleosomal map from total H3 ChIP–seq data in NAc after saline or repeated cocaine treatment (Fig. 1A, 3A). We identified over 130,000 occupancy changes (altered density of nucleosomes) and 10,000 shift changes (altered position of nucleosomes), consistent with dynamic nucleosome remodeling in NAc after repeated cocaine exposure (Fig. 3B, 3C; lists of nucleosome remodeling chromosomal sites after repeated cocaine exposure is available at http://neuroscience.mssm.edu/nestler/nidappg/chromatingenedatabase.html). There were slightly more increased nucleosome occupancy events (76,574) compared to decreased nucleosome occupancy event (55851) following cocaine treatment (Fig. 3B). All nucleosome occupancy and shift events occurred throughout the genome, with approximately 2/3 of both seen in intergenic regions and the rest occurring in genic regions (Fig. 3B, 3C). Among the genes that were found to be affected at the level of nucleosome remodeling after repeated cocaine exposure (http://neuroscience.mssm.edu/nestler/nidappg/chromatingenedatabase.html) are many that have already been implicated in models of cocaine addiction. These genes include those that encode CREB and Fos/Jun transcription factors, AMPA and NMDA glutamate receptor subunits, GABA receptor subunits, calcium/calmodulin-dependent protein kinases, brain-derived neurotrophic factors (BDNF), and even epigenetic regulators including nucleosome remodeling factors themselves (Robison and Nestler, 2011, Jonkman and Kenny, 2013, Zhou et al., 2014).

Discussion

Results from the present study suggest that acute cocaine exposure increased *Baz1a* expression in NAc while repeated cocaine exposure produced the opposite effect. The decrease in BAZ1A after repeated cocaine exposure was mirrored in NAc of human cocaine-addicted subjects. Consistent with previous report of G9a downregulation after repeated cocaine (Maze et al., 2010), the downregulation of BAZ1A, typically known for its transcriptionally repressive activity (Shogren-Knaak et al., 2006), may contribute to regulation of the battery of genes that display sensitized transcriptional responses after repeated cocaine administration. Additionally, we showed that the overexpression of BAZ1A in NAc reduces cocaine CPP. This suggests that increased *Baz1a* expression in NAc with initial exposure to cocaine may counteract rewarding responses to the drug. In contrast, with persistent exposure, suppression of BAZ1A would be expected to enhance cocaine reward.

Previous work showed that persistent induction of BAZ1A in NAc increases animals' susceptibility to stress (Sun et al., 2015). Together, these findings suggest a role for NAc BAZ1A in mediating dysregulation of the reward circuitry: persistent upregulation after stress leads to depressive-like behavior, while downregulation after repeated cocaine exposure leads to increased susceptibility to cocaine reward.

Interestingly, another accessory ISWI subunit, BAZ1B, is also regulated in NAc by cocaine and stress: BAZ1B is upregulated by repeated cocaine exposure and selectively upregulated in animals resistant to stress, and promotes cocaine reward and stress resilience (Sun et al., 2016). Although the exact complexes formed by these proteins to remodel nucleosomes remain controversial, both BAZ1A and BAZ1B exert at least some of their effects through association with SMARCA5, the active ATPase of the ISWI remodeling complexes (Sun et al., 2015, Sun et al., 2016). This suggest that transcriptional regulation of these distinct accessory proteins, with the resulting formation of slightly different chromatin remodeling complexes, can have vastly different behavioral outcomes. Investigation of the gene targets of these distinct complexes is an important goal for future studies.

While no animal model can recapitulate the entire spectrum of drug addiction in humans, various models measure different aspects of addiction-related behavior including drug sensitization, reward, and relapse (Lynch et al., 2010, Steketee and Kalivas, 2011). It is interesting that BAZ1A overexpression in NAc differentially regulates two cocaine-related behaviors: it reduces cocaine reward as measured by CPP while enhancing cocaine-induced locomotor activity. CPP assesses the rewarding effects of drug and examines the context-specific nature of drug reward, while locomotor activity provides a measure of enhanced psychomotor responses to a drug after repeated exposure. Previous studies have shown that these two measures are distinct and are regulated by partly different mechanisms (Eisener-Dorman et al., 2011). It is also possible that the different doses of cocaine used for the different paradigms may contribute to differential effects of BAZ1A overexpression.

Nucleosome maps before and after repeated cocaine exposure suggest that there is dynamic nucleosome remodeling as a result of cocaine administration. While there has been some initial suggestion as to the exact role of BAZ1A in nucleosome repositioning, further studies in more dissectible systems need to be performed to better interpret these nucleosome positioning data (Sun et al., 2015). Nonetheless, the extensive nature of the nucleosome remodeling suggests that other complexes are likely involved and preliminary data (not shown) suggests that indeed other nucleosome remodeling proteins are regulated in response to repeated cocaine exposure.

Together, results of the present study establish that NAc BAZ1A and nucleosome remodeling are important for the regulation of behavioral responses to cocaine. While more studies are necessary to further characterize the mechanisms and targets of BAZ1A-containing nucleosome remodeling complexes, these findings will guide future investigations aimed at better understanding the biological basis of cocaine-related disorders.

Acknowledgments

The work was supported by NIDA (P01DA008227).

References

Chen K, Xi Y, Pan X, Li Z, Kaestner K, Tyler J, Dent S, He X, Li W. DANPOS: dynamic analysis of nucleosome position and occupancy by sequencing. Genome Res. 2013; 23:341–351. [PubMed: 23193179]

Clapier CR, Cairns BR. The biology of chromatin remodeling complexes. Annu Rev Biochem. 2009; 78:273–304. [PubMed: 19355820]

Covington HE 3rd, Maze I, Sun H, Bomze HM, DeMaio KD, Wu EY, Dietz DM, Lobo MK, Ghose S, Mouzon E, Neve RL, Tamminga CA, Nestler EJ. A role for repressive histone methylation in cocaine-induced vulnerability to stress. Neuron. 2011; 71:656–670. [PubMed: 21867882]

Damez-Werno DM, Sun H, Scobie KN, Shao N, Rabkin J, Dias C, Calipari ES, Maze I, Pena CJ, Walker DM, Cahill ME, Chandra R, Gancarz A, Mouzon E, Landry JA, Cates H, Lobo MK, Dietz D, Allis CD, Guccione E, Turecki G, Defilippi P, Neve RL, Hurd YL, Shen L, Nestler EJ. Histone arginine methylation in cocaine action in the nucleus accumbens. Proceedings of the National Academy of Sciences of the United States of America. 2016; 113:9623–9628. [PubMed: 27506785]

Deng JV, Wan Y, Wang X, Cohen S, Wetsel WC, Greenberg ME, Kenny PJ, Calakos N, West AE. MeCP2 phosphorylation limits psychostimulant-induced behavioral and neuronal plasticity. The Journal of neuroscience : the official journal of the Society for Neuroscience. 2014; 34:4519–4527. [PubMed: 24671997]

Eisener-Dorman AF, Grabowski-Boase L, Tarantino LM. Cocaine locomotor activation, sensitization and place preference in six inbred strains of mice. Behav Brain Funct. 2011; 7:29. [PubMed: 21806802]

Feng J, Shao N, Szulwach KE, Vialou V, Huynh J, Zhong C, Le T, Ferguson D, Cahill ME, Li Y, Koo JW, Ribeiro E, Labonte B, Laitman BM, Estey D, Stockman V, Kennedy P, Courousse T, Mensah I, Turecki G, Faull KF, Ming GL, Song H, Fan G, Casaccia P, Shen L, Jin P, Nestler EJ. Role of Tet1 and 5-hydroxymethylcytosine in cocaine action. Nature neuroscience. 2015; 18:536–544. [PubMed: 25774451]

Feng J, Wilkinson M, Liu X, Purushothaman I, Ferguson D, Vialou V, Maze I, Shao N, Kennedy P, Koo J, Dias C, Laitman B, Stockman V, LaPlant Q, Cahill ME, Nestler EJ, Shen L. Chronic cocaine-regulated epigenomic changes in mouse nucleus accumbens. Genome biology. 2014; 15:R65. [PubMed: 24758366]

Jonkman S, Kenny PJ. Molecular, cellular, and structural mechanisms of cocaine addiction: a key role for microRNAs. Neuropsychopharmacology : official publication of the American College of Neuropsychopharmacology. 2013; 38:198–211. [PubMed: 22968819]

LaPlant Q, Vialou V, Covington HE 3rd, Dumitriu D, Feng J, Warren BL, Maze I, Dietz DM, Watts EL, Iniguez SD, Koo JW, Mouzon E, Renthal W, Hollis F, Wang H, Noonan MA, Ren Y, Eisch AJ, Bolanos CA, Kabbaj M, Xiao G, Neve RL, Hurd YL, Oosting RS, Fan G, Morrison JH, Nestler EJ. Dnmt3a regulates emotional behavior and spine plasticity in the nucleus accumbens. Nature neuroscience. 2010; 13:1137–1143. [PubMed: 20729844]

Lynch WJ, Nicholson KL, Dance ME, Morgan RW, Foley PL. Animal models of substance abuse and addiction: implications for science, animal welfare, and society. Comp Med. 2010; 60:177–188. [PubMed: 20579432]

Malvaez M, McQuown SC, Rogge GA, Astarabadi M, Jacques V, Carreiro S, Rusche JR, Wood MA. HDAC3-selective inhibitor enhances extinction of cocaine-seeking behavior in a persistent manner. Proceedings of the National Academy of Sciences of the United States of America. 2013; 110:2647–2652. [PubMed: 23297220]

Maze I, Covington HE 3rd, Dietz DM, LaPlant Q, Renthal W, Russo SJ, Mechanic M, Mouzon E, Neve RL, Haggarty SJ, Ren Y, Sampath SC, Hurd YL, Greengard P, Tarakhovsky A, Schaefer A, Nestler EJ. Essential role of the histone methyltransferase G9a in cocaine-induced plasticity. Science. 2010; 327:213–216. [PubMed: 20056891]

Narlikar GJ, Sundaramoorthy R, Owen-Hughes T. Mechanisms and functions of ATP-dependent chromatin-remodeling enzymes. Cell. 2013; 154:490–503. [PubMed: 23911317]

Renthal W, Maze I, Krishnan V, Covington HE 3rd, Xiao G, Kumar A, Russo SJ, Graham A, Tsankova N, Kippin TE, Kerstetter KA, Neve RL, Haggarty SJ, McKinsey TA, Bassel-Duby R, Olson EN,

Nestler EJ. Histone deacetylase 5 epigenetically controls behavioral adaptations to chronic emotional stimuli. Neuron. 2007; 56:517–529. [PubMed: 17988634]

Robison AJ, Nestler EJ. Transcriptional and epigenetic mechanisms of addiction. Nature reviews Neuroscience. 2011; 12:623–637. [PubMed: 21989194]

Rogge GA, Singh H, Dang R, Wood MA. HDAC3 is a negative regulator of cocaine-context-associated memory formation. The Journal of neuroscience : the official journal of the Society for Neuroscience. 2013; 33:6623–6632. [PubMed: 23575859]

Sala A, Toto M, Pinello L, Gabriele A, Di Benedetto V, Ingrassia AM, Lo Bosco G, Di Gesu V, Giancarlo R, Corona DF. Genome-wide characterization of chromatin binding and nucleosome spacing activity of the nucleosome remodelling ATPase ISWI. EMBO J. 2011; 30:1766–1777. [PubMed: 21448136]

Sartor GC, Powell SK, Brothers SP, Wahlestedt C. Epigenetic Readers of Lysine Acetylation Regulate Cocaine-Induced Plasticity. The Journal of neuroscience : the official journal of the Society for Neuroscience. 2015; 35:15062–15072. [PubMed: 26558777]

Scobie KN, Damez-Werno D, Sun H, Shao N, Gancarz A, Panganiban CH, Dias C, Koo J, Caiafa P, Kaufman L, Neve RL, Dietz DM, Shen L, Nestler EJ. Essential role of poly(ADP-ribosyl)ation in cocaine action. Proceedings of the National Academy of Sciences of the United States of America. 2014; 111:2005–2010. [PubMed: 24449909]

Shogren-Knaak M, Ishii H, Sun JM, Pazin MJ, Davie JR, Peterson CL. Histone H4-K16 acetylation controls chromatin structure and protein interactions. Science. 2006; 311:844–847. [PubMed: 16469925]

Steketee JD, Kalivas PW. Drug wanting: behavioral sensitization and relapse to drug-seeking behavior. Pharmacol Rev. 2011; 63:348–365. [PubMed: 21490129]

Sun H, Damez-Werno DM, Scobie KN, Shao NY, Dias C, Rabkin J, Koo JW, Korb E, Bagot RC, Ahn FH, Cahill ME, Labonte B, Mouzon E, Heller EA, Cates H, Golden SA, Gleason K, Russo SJ, Andrews S, Neve R, Kennedy PJ, Maze I, Dietz DM, Allis CD, Turecki G, Varga-Weisz P, Tamminga C, Shen L, Nestler EJ. ACF chromatin-remodeling complex mediates stress-induced depressive-like behavior. Nature medicine. 2015; 21:1146–1153.

Sun H, Martin JA, Werner CT, Wang ZJ, Damez-Werno DM, Scobie KN, Shao NY, Dias C, Rabkin J, Koo JW, Gancarz AM, Mouzon EA, Neve RL, Shen L, Dietz DM, Nestler EJ. BAZ1B in Nucleus Accumbens Regulates Reward-Related Behaviors in Response to Distinct Emotional Stimuli. The Journal of neuroscience : the official journal of the Society for Neuroscience. 2016; 36:3954–3961. [PubMed: 27053203]

Vogel-Ciernia A, Matheos DP, Barrett RM, Kramar EA, Azzawi S, Chen Y, Magnan CN, Zeller M, Sylvain A, Haettig J, Jia Y, Tran A, Dang R, Post RJ, Chabrier M, Babayan AH, Wu JI, Crabtree GR, Baldi P, Baram TZ, Lynch G, Wood MA. The neuron-specific chromatin regulatory subunit BAF53b is necessary for synaptic plasticity and memory. Nature neuroscience. 2013; 16:552–561. [PubMed: 23525042]

Whitehouse I, Rando OJ, Delrow J, Tsukiyama T. Chromatin remodelling at promoters suppresses antisense transcription. Nature. 2007; 450:1031–1035. [PubMed: 18075583]

Wright KN, Hollis F, Duclot F, Dossat AM, Strong CE, Francis TC, Mercer R, Feng J, Dietz DM, Lobo MK, Nestler EJ, Kabbaj M. Methyl supplementation attenuates cocaine-seeking behaviors and cocaine-induced c-Fos activation in a DNA methylation-dependent manner. The Journal of neuroscience : the official journal of the Society for Neuroscience. 2015; 35:8948–8958. [PubMed: 26063926]

Yen K, Vinayachandran V, Batta K, Koerber RT, Pugh BF. Genome-wide nucleosome specificity and directionality of chromatin remodelers. Cell. 2012; 149:1461–1473. [PubMed: 22726434]

Zhou Z, Enoch MA, Goldman D. Gene expression in the addicted brain. International review of neurobiology. 2014; 116:251–273. [PubMed: 25172478]

Highlights

- BAZ1A is downregulated in the NAc of mice exposed repeatedly to cocaine
- BAZ1A is downregulated in the NAc of cocaine-addicted humans
- Overexpression of BAZ1A in mouse NAc reduces cocaine reward as assessed by CPP
- Overexpression of BAZ1A in mouse NAc increases cocaine-induced locomotor activation
- Genome-wide nucleosome occupancy and shift changes after repeated cocaine exposure

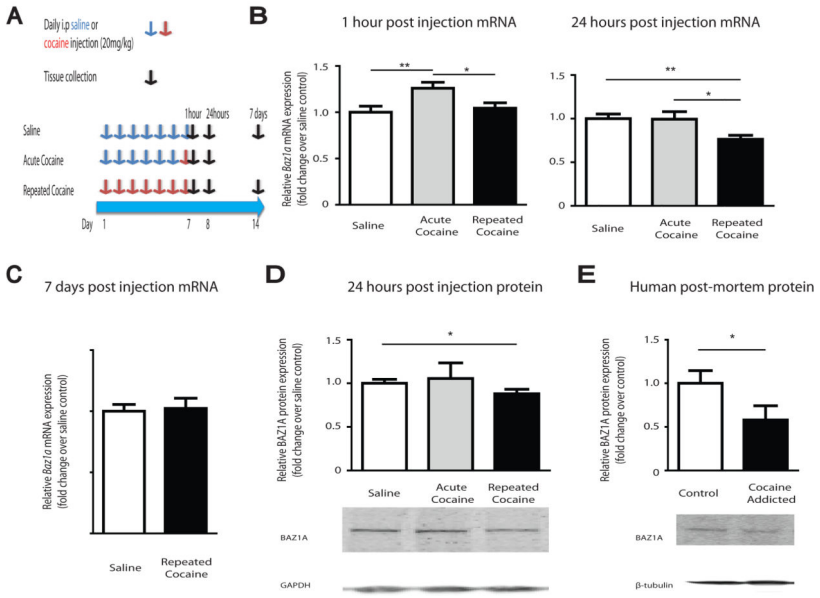

Fig. 1.

Regulation of BAZ1A in NAc after cocaine exposure in mice and humans. (A) Intraperitoneal (i.p.) saline/cocaine injection paradigm in mice. Saline: 7 daily saline injections. Acute cocaine: 6 daily saline injections followed by a single cocaine injection (20 mg/kg) on day 7. Repeated cocaine: 7 daily cocaine injections (20 mg/kg). (B) *Baz1a* mRNA levels in NAc 1 and 24 hours after saline, acute cocaine, and repeated cocaine treatment. (C) *Baz1a* mRNA levels in NAc 7 days after repeated saline or cocaine treatment. (D) BAZ1A protein levels in NAc 24 hours after saline, acute cocaine, and repeated cocaine treatment. (E) BAZ1A protein levels in NAc of postmortem human cocaine-addicted subjects compared to controls. * P<0.05, ** P<0.01 in respective comparisons.

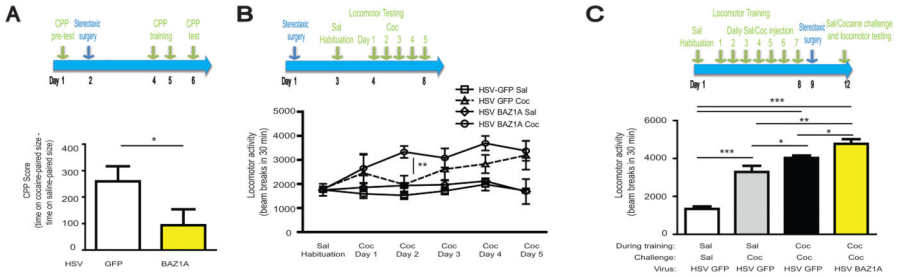

Fig. 2.

BAZ1A in NAc controls cocaine-induced behaviors. Experimental paradigms are shown above each panel. (A) BAZ1A overexpression in NAc reduces cocaine reward as measured by CPP. (B) BAZ1A overexpression in NAc enhances cocaine-induced locomotor activity. (C) BAZ1A overexpression in NAc further enhances increased locomotor activity following a cocaine challenge. * P< 0.05 ** $P < 0.01$, *** $P < 0.001$ in respective comparisons.

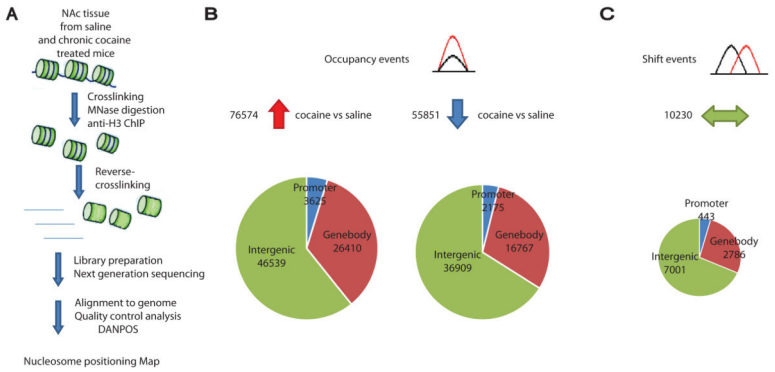

Fig. 3.

Regulation of nucleosome positioning in NAc by cocaine. (A) Workflow for generation of nucleosome positioning maps in NAc after saline or repeated cocaine treatment. (B) Genome–wide identification of nucleosome occupancy changes after repeated cocaine vs saline controls. (C) Genome–wide identification of nucleosome shift events after repeated cocaine vs saline controls.