Published in final edited form as:

Biol Psychiatry. 2017 April 01; 81(7): 550–551. doi:10.1016/j.biopsych.2017.01.007.

Nuclear Arc Puts a Brake on Cocaine-Induced Chromatin Remodeling and Behaviors

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Psychostimulants, including cocaine, cause molecular adaptations in the nucleus of neurons, which include chromatin remodeling and altered gene transcription (1). These molecular adaptations have profound effects at the levels of the cell and circuitry, and ultimately in behavioral output (1). Numerous studies demonstrate altered transcription and chromatin remodeling in brain reward regions, including the striatum, after repeated or acute cocaine exposure (1–4). While there has been much investigation into chromatin remodeling and its effects on gene transcription after exposure to cocaine, there is minimal information into the mechanisms that underlie the alterations in chromatin organization. In this issue of *Biological Psychiatry*, Salery *et al.* (5) provide new insight into this by examining a role for striatal nuclear accumulation of activity-regulated cytoskeleton-associated protein (Arc) on chromatin remodeling, as well as behavior, in response to cocaine exposure.

Numerous studies identify Arc as an immediate early gene (IEG), a set of genes that are transiently induced immediately after a stimulus, such as cocaine. Arc belongs to the group of effector protein IEGs that alter cellular processes in contrast to transcription factor IEGs, such as c-Fos and FosB (2). Arc accumulates in dendritic compartments, resulting in altered synaptic processes (6). However, there is evidence for Arc accumulation in the nucleus, and Arc contains regions that control its nuclear accumulation, including a nuclear localization signal, a nuclear retention domain, and a nuclear export signal (7). The function of Arc in the nucleus is unclear, as it has been demonstrated to have both a permissive and a repressive role on transcription (7,8). Further, although Arc is induced in striatum after cocaine exposure (2), the role of Arc in striatal neurons after cocaine is not well studied. In this issue, Salery *et al.* (5) provide data for a new mechanistic role of Arc in striatal neuron nuclei after cocaine exposure.

The authors demonstrate that Arc messenger RNA and protein are induced by an acute injection of cocaine in striatal regions, which includes the dorsomedial striatum and the ventral striatum, known as nucleus accumbens. Similar to the characteristic transient induction of IEGs, Arc induction peaks at 30 and 60 minutes, returning to baseline 2 hours after the cocaine injection. Arc expression requires protein synthesis because anisomycin, a

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Disclosures

The author reports no biomedical financial interests or potential conflicts of interest.

protein synthesis inhibitor, prevents Arc induction by cocaine. Further, Arc induction is dependent on extracellular signal-related kinase (ERK) and occurs downstream of *N*-methyl-D-aspartate glutamate receptors and dopamine 1 (D₁) receptors, the latter implicating that Arc could be induced in striatal D₁-expressing medium spiny neuron (MSN) subtypes. This is consistent with cocaine-mediated induction of IEGs and phosphorylated ERK in D₁-MSNs and a study demonstrating that cocaine induction of Arc occurs through D₁ signaling (2–4).

Salery *et al.* (5) demonstrate that the induction of Arc occurs in the neuropile, consistent with its role in synaptic processes (6), but interestingly also observed a robust accumulation of Arc in the nucleus. Further analysis of Arc accumulation in the nucleus after cocaine revealed an exclusion of Arc from heterochromatin, regions where DNA is tightly packed into chromatin and gene transcription is inactive. Instead Arc was highly colocalized with histone H3 phosphorylated at serine 10 (Ser-10-Histone pH3), a marker of nucleosomal response that results in chromatin remodeling toward a transcriptional permissive state. Based on the Arc accumulation in the nucleus of striatal neurons and its colocalization at active transcriptional zones, Salery *et al.* (5) hypothesized that nuclear Arc is regulating chromatin remodeling. To further examine Arc's effect on chromatin organization they performed live imaging on striatal neuron cultures transfected with an Arc–green fluorescent protein (GFP) DNA construct and treated the cultures with glutamate to induce phosphorylation of histone 3 (pH3). While striatal neurons transfected with GFP alone display pH3 induction, this is blocked in Arc-GFP-expressing striatal neurons. These findings implicate that nuclear Arc blunts nucleosomal response, thus inhibiting chromatin remodeling that is permissive for gene transcription.

To further demonstrate the role for nuclear Arc in chromatin remodeling, Salery *et al.* used mice in which GFP replaces the Arc coding sequence, GFP-Arc knockin (KI) mice (9). In these mice Arc is not expressed but instead GFP acts as a reporter for Arc promoter activity. In a wild-type condition, acute cocaine caused a reduction of heterochromatin in striatal neurons. Interestingly, GFP-Arc KI mice displayed reduced heterochromatin in saline conditions, which was further reduced by cocaine. Thus, Arc deletion results in a shift toward reduced DNA compaction, with chromatin organization favoring permissive transcription. To assess transcriptional activation with loss of Arc, Salery *et al.* examined the activated form of RNA polymerase II (RNA Pol II), a critical component of the nuclear transcriptional machinery. In the wild-type condition phosphorylated RNA Pol II was increased in striatal neurons after cocaine exposure. Arc-GFP KI mice showed an increase in active RNA Pol II in striatal neurons in basal conditions, which was not further increased with cocaine, suggesting that RNA Pol II activity has reached a threshold in the basal condition with loss of Arc, which cannot be further activated by cocaine. The findings from the Salery *et al.* study indicate that Arc may act as a negative regulator of RNA Pol II activity, which could be a consequence of Arc dampening chromatin remodeling to a less permissive transcriptional state.

Finally, Salery *et al.* tested whether the deletion of Arc can alter cocaine-mediated behavioral states. The authors showed that Arc deletion results in enhanced locomotor sensitization to a second dose of cocaine compared with the wild-type condition.

Additionally, this second dose of cocaine augments the induction of c-Fos–positive neurons when Arc is absent. An alteration in c-Fos activity to cocaine in Arc-deficient mice is consistent with studies demonstrating c-Fos induction occurring during behavioral sensitization (3,4). Consistent with the enhanced sensitized locomotor response to cocaine observed in GFP-Arc KI mice, these mice also display increased preference for a cocaine-paired chamber in a conditioned place preference paradigm.

Altogether the results from the Salery *et al.* (5) study indicate that Arc deletion enhanced behavioral responses to cocaine, which plausibly occurs through altered chromatin remodeling to permissive transcriptional states in striatal neurons. Thus, when animals are exposed to cocaine, Arc can act as a brake on permissive transcription through dampening chromatin remodeling, leaving DNA in compacted inactive states. It is plausible that this blunting of transcription may prevent further transcriptional regulation of genes that drive behavioral states to cocaine. Thus, Arc serves as a homeostatic regulator of cocaine-induced behavioral plasticity through its homeostatic regulation of chromatin dynamics.

The mechanism by which Arc regulates chromatin dynamics is unclear. Arc is known to interact with cytoskeletal molecules, and there is no evidence of Arc binding to DNA (7); thus, it is likely altering chromatin remodeling through indirect mechanisms. Indeed, as Salery *et al.* (5) noted, Arc interacts with promyelocytic leukemia bodies, which regulate transcriptional machinery and histone acetylation through control of histone acetyltransferase activity (7,8). Future investigation into the impact of Arc on promyelocytic leukemia bodies and downstream transcriptional regulation in cocaine conditions could provide more mechanistic insight into how Arc is altering chromatin dynamics.

Additionally, insight into Arc and its nuclear role through promyelocytic leukemia bodies in chronic cocaine conditions could be beneficial for further understanding the neurobiological mechanisms that underlie the shift from initial drug use to persistent drug use. The current study focuses on a role for Arc in acute cocaine conditions. However, it would be interesting if a similar mechanism for Arc occurs with chronic cocaine and in contingent cocaine behavioral paradigms in which an animal is actively taking cocaine. After abstinence from chronic psychostimulants, the induction of the IEG c-Fos becomes desensitized (10). It is unclear if this desensitization also occurs with Arc. If so, a reduction of Arc expression could be a mechanism by which chronic cocaine leads to augmented chromatin remodeling to further increase permissive transcription of genes regulating the persistent behavioral outcomes associated with long-term cocaine exposure.

Along with assessment of nuclear Arc in chronic cocaine conditions, an analysis of Arc in specific neuron subtypes could provide a further insight into its role within reward circuits. The striatum is a heterogeneous brain region mainly composed of the two projection MSN subtypes, enriched in either D₁ or dopamine 2 receptors and other differentially enriched genes (4). This current study did not assess specific neuron subtypes, but much of the data in this study are consistent with changes observed in D1-MSNs after cocaine exposure. This includes p38 and c-Fos induction after cocaine, which occurs in D1-MSNs, as well as ERK-mediated Arc induction, because phosphorylated ERK is enhanced in D1-MSNs with acute

cocaine (3,4). Further, the current study and a previous study show that cocaine induction of Arc is mediated through D₁ signaling (2,5).

Overall the study by Salery *et al.* (5) demonstrates a novel role for nuclear Arc in regulating chromatin dynamics. The study implicates nuclear Arc as a molecular brake for chromatin remodeling toward inactive transcription, thus acting as a homeostatic regulator of chromatin organization and ultimately behavioral responses to cocaine. Further understanding into these mechanisms of Arc to dampen cocaine-induced transcription and behavior could provide novel therapeutic approaches for psychostimulant abuse.

References

1. Robison AJ, Nestler EJ. 2011; Transcriptional and epigenetic mechanisms of addiction. *Nat Rev Neuroscience*. 12:623–637. [PubMed: 21989194]
2. Fosnaugh JS, Bhat RV, Yamagata K, Worley PF, Baraban JM. 1995; Activation of arc, a putative “effector” immediate early gene, by cocaine in rat brain. *J Neurochem*. 64:2377–2380. [PubMed: 7722525]
3. Bertran-Gonzalez J, Bosch C, Maroteaux M, Matamalas M, Herve D, Valjent E, Girault JA. 2008; Opposing patterns of signaling activation in dopamine D1 and D2 receptor-expressing striatal neurons in response to cocaine and haloperidol. *J Neurosci*. 28:5671–5685. [PubMed: 18509028]
4. Lobo MK, Nestler EJ. 2011; The striatal balancing act in drug addiction: Distinct roles of direct and indirect pathway medium spiny neurons. *Front Neuroanat*. 5:41. [PubMed: 21811439]
5. Salery M, Dos Santos M, Saint-Jour E, Moumné L, Pagès C, Kappès V, et al. 2017; Activity-regulated cytoskeleton-associated protein accumulates in the nucleus in response to cocaine and acts as a brake on chromatin remodeling and long-term behavioral alterations. *Biol Psychiatry*. 81:573–584. [PubMed: 27567310]
6. Lyford GL, Yamagata K, Kaufmann WE, Barnes CA, Sanders LK, Copeland NG, et al. 1995; Arc, a growth factor and activity-regulated gene, encodes a novel cytoskeleton-associated protein that is enriched in neuronal dendrites. *Neuron*. 14:433–445. [PubMed: 7857651]
7. Korb E, Wilkinson CL, Delgado RN, Lovero KL, Finkbeiner S. 2013; Arc in the nucleus regulates PML-dependent GluA1 transcription and homeostatic plasticity. *Nat Neurosci*. 16:874–883. [PubMed: 23749147]
8. Wee, Cl; Teo, S; Oey, NE; Wright, GD; VanDongen, HM; VanDongen, AM. 2014; Nuclear Arc interacts with histone acetyltransferase tip60 to modify H4K12 acetylation(1,2,3). *eNeuro*. 1
9. Wang KH, Majewska A, Schummers J, Farley B, Hu C, Sur M, et al. 2006; In vivo two-photon reveals a role of arc in enhancing orientation specificity in visual cortex. *Cell*. 126:389–402. [PubMed: 16873068]
10. Renthal W, Carle TL, Maze I, Covington HE 3rd, Truong HT, Alibhai I, et al. 2008; Delta FosB mediates epigenetic desensitization of the c-fos gene after chronic amphetamine exposure. *J Neurosci*. 28:7344–7349. [PubMed: 18632938]