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# From Signaling Molecules to Circuits and Behaviors: Cell-Type–Specific Adaptations to Psychostimulant Exposure in the Striatum

Marine Sallery, Pierre Trifilieff, Jocelyne Caboche, and Peter Vanhoutte

## ABSTRACT

Addiction is characterized by a compulsive pattern of drug seeking and consumption and a high risk of relapse after withdrawal that are thought to result from persistent adaptations within brain reward circuits. Drugs of abuse increase dopamine (DA) concentration in these brain areas, including the striatum, which shapes an abnormal memory trace of drug consumption that virtually hijacks reward processing. Long-term neuronal adaptations of gamma-aminobutyric acidergic striatal projection neurons (SPNs) evoked by drugs of abuse are critical for the development of addiction. These neurons form two mostly segregated populations, depending on the DA receptor they express and their output projections, constituting the so-called direct (D<sub>1</sub> receptor) and indirect (D<sub>2</sub> receptor) SPN pathways. Both SPN subtypes receive converging glutamate inputs from limbic and cortical regions, encoding contextual and emotional information, together with DA, which mediates reward prediction and incentive values. DA differentially modulates the efficacy of glutamate synapses onto direct and indirect SPN pathways by recruiting distinct striatal signaling pathways, epigenetic and genetic responses likely involved in the transition from casual drug use to addiction. Herein we focus on recent studies that have assessed psychostimulant-induced alterations in a cell-type–specific manner, from remodeling of input projections to the characterization of specific molecular events in each SPN subtype and their impact on long-lasting behavioral adaptations. We discuss recent evidence revealing the complex and concerted action of both SPN populations on drug-induced behavioral responses, as these studies can contribute to the design of future strategies to alleviate specific behavioral components of addiction.

**Keywords:** Addiction, Dopamine receptor, Gene regulation, Signaling, Striatal projection neuron, Striatum

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Drug addiction is defined as a compulsive pattern of drug-seeking and drug-taking behavior, with recurrent episodes of abstinence and relapse, and a loss of control despite negative consequences. A current hypothesis is that persistent behavioral alterations characterizing addiction result from drug-evoked long-term changes in synaptic efficacy involving the early recruitment of specific signaling cascade and gene expression (1). This continuum between synaptic and nuclear events shapes an enduring remodeling of the reward circuitry likely involved in the transition from casual drug use to addiction (2–4). This drug-induced memory trace is persistent and tightly related to the context of drug consumption, partly explaining the high risk of relapse even after long periods of abstinence. Addictive drugs promote reinforcement by increasing dopamine (DA) in the mesocorticolimbic system (5), which alters excitatory glutamate transmission within the reward circuitry and hijacks reward processing (1). The striatum is a key target structure of drugs of abuse because it is at the crossroad of converging glutamate inputs from limbic, thalamic, and cortical regions, which encode components of drug-associated stimuli and environment, and DA, which mediates reward prediction error and incentive values. These

signals are integrated in gamma-aminobutyric acidergic striatal projection neurons (SPNs), which receive glutamate and DA axons converging onto their dendritic spines (6,7). SPNs primarily form two mostly distinct populations based on the expression of either DA D<sub>1</sub> receptors (D<sub>1</sub>Rs) or D<sub>2</sub> receptors (D<sub>2</sub>Rs) (8,9) which are G protein–coupled receptors positively and negatively modulating adenylyl cyclase through their respective coupling to G<sub>s/oif</sub> and G<sub>i/o</sub> subtypes (10,11). While a classical view is that the two populations of SPNs act in parallel, playing antagonistic functional roles, the picture seems much more complex, as discussed below.

Initial studies based on the use of DA receptor agonists or antagonists led to somewhat confounding results on the role of D1R-SPNs and D2R-SPNs in drug-evoked adaptations (12). A major limitation of such strategies is the widespread effect of these compounds in the brain, with different specificity, pharmacokinetics, and downstream effects relative to presynaptic and postsynaptic receptors. Analyzing molecular events in identified neuronal populations was made possible by the development of reporter mouse lines expressing fluorescent proteins or Cre-recombinase under the control of cell-specific promoters *drd1a* and *drd2/adora2a* for D1R-SPNs and D2R-

SPNs, respectively (13–17). From circuits to molecules, cell-type-specific manipulations are now achievable owing to targeted chemogenetic and optogenetic technologies, conditional knockout, or acting on specific protein-protein interactions. This deepened our understanding of the differential impact of drug exposure on these two neuronal populations, from alterations of the inputs they receive to the pattern of signaling cascades and transcriptional landscape they exhibit at various stages of addiction. Focusing on studies using the psychostimulants cocaine and amphetamine, which constitute the vast majority of the work regarding cell-specific functions in addiction, we discuss the literature linking drug-induced behavioral alterations with adaptations in D1R-SPNs and D2R-SPNs at the circuit, cellular, and molecular levels.

### CELL-TYPE-SPECIFIC MODULATION OF SPN ACTIVITY

A current hypothesis is that the transition from recreational to compulsive drug use relies on a gradual recruitment from ventromedial to dorsolateral striatal subregions (18,19). Despite the existence of behavioral features of vulnerability toward addiction (19), few preclinical studies support the intriguing possibility that individuals who develop behavioral traits of addiction display plasticity-related alterations in the striatum (20). Nonetheless, most studies have focused on remodeling of neural circuits in the ventral striatum (i.e., nucleus accumbens [NAc]) and dorsomedial striatum (DMS) induced by early drug exposure (Supplemental Table S1), which does not reflect addiction per se but might constitute a main trigger toward drug abuse.

SPNs constitute 95% of striatal neurons, the remaining 5% being local interneurons, which include large tonically active cholinergic interneurons. Even though cholinergic interneurons are major players in the modulation of striatal microcircuits (21), their implication in drug responses is beyond the scope of the current review.

In the dorsal striatum (DS), a common view is that D1R-SPNs and D2R-SPNs exert opposite effects through distinct output projections, with D2R-SPN reaching the midbrain through polysynaptic projections via the external globus pallidus (indirect pathway), while D1R-SPN directly project onto the internal globus pallidus and the substantia nigra (direct pathway). However, a subset of D1R-SPNs displays projections to the globus pallidus (22), which can be augmented under certain conditions (23). This dichotomy becomes even more erroneous regarding the NAc because 2% to 5% of core SPNs express both DA receptors (24,25), while in the shell, this proportion varies from 2% to 5% (25) up to 10% to 15% (24), depending on the methodologies used. Moreover, even though there exists a recent controversy as to whether they constitute a distinct subpopulation or they form collaterals, a large proportion of NAc D1R-SPNs projects in the ventral pallidum (VP), which is the canonical output of D2R-SPNs (25–27).

Consistent with the so-called Go/NoGo model of basal ganglia in which D1R-SPN activity facilitates and D2R-SPN activity inhibits movement planning/initiation (28–30), cell-type-specific manipulations initially supported that SPNs from the NAc and DMS play antagonistic roles on reward processing, including drug-induced behaviors (31,32). Indeed, the selective ablation of NAc D2R-SPNs (17) or their transient

chemogenetic inhibition in the DS (33) enhances psychostimulant-induced conditioned place preference (CPP) and locomotor sensitization, respectively. Conversely, D2R-SPN chemogenetic activation in the entire striatum blocks amphetamine-induced sensitization (34), while their optogenetic stimulation in the NAc reduces cocaine CPP (31) and alleviates locomotor sensitization when applied during the withdrawal period (35). On the other hand, optogenetic activation of NAc D1R-SPNs enhances cocaine-induced CPP (31), whereas their inhibition in the DS (33) or the NAc (36,37) or their reversible blockade in the entire striatum (38) decreases psychostimulant-induced locomotor sensitization or CPP. Regarding operant behavior, NAc D2R-SPN chemogenetic inhibition enhances motivation to obtain cocaine, whereas their activation by optogenetics diminishes drug seeking (39). Conversely, chemogenetic inhibition of D1R-SPNs in the DMS reduces cue-induced reinstatement of cocaine seeking while sparing escalation, maintenance, and incentive components (40).

Altogether, these studies support a binary model in which D1R-SPNs and D2R-SPNs primarily form two parallel pathways promoting and reducing psychostimulant-induced adaptations, respectively. However, this dichotomic view overlooks several anatomofunctional findings. Notably, selective inhibition of NAc D1R-SPN projections to the VP reduces cue-induced reinstatement of cocaine seeking, suggesting that specific D1R-SPN projections might control distinct components of addictive behaviors (26). Accordingly, stimulating NAc shell projections to lateral hypothalamus [likely originating from D1R-SPNs (41)] enhances the motivation to self-administer cocaine and facilitates drug seeking, while global NAc shell activation accelerates extinction of this behavior (42). This latter finding could result from the concomitant stimulation of both SPN populations, which is likely to differentially impact striatal microcircuits. Along the same line, the “lateral inhibition” of D2R-SPNs onto D1R-SPNs in the NAc appears as a major mechanism by which D2R-SPNs could participate to locomotor sensitization by favoring D1R-SPN activity (43,44). Moreover, cocaine can inhibit D2R-SPN synaptic transmission onto VP neurons in a DA-independent but serotonin-dependent manner (45), the behavioral consequences of which remain unknown. Functionally, other findings challenge the view of opposite actions of the two SPN populations on drug-induced behavioral adaptations. In the DMS, ablation of D1R-SPNs decreases acute amphetamine-induced locomotor response without affecting sensitization, whereas ablating D2R-SPNs decreases sensitization but spares acute locomotor responses (46). Similarly, the transient inhibition of synaptic transmission of D2R-SPNs in the DMS delays the development of locomotor sensitization, although to a lower extent than D1R-SPN inhibition does (38).

Studies on the control of nondrug reward processing reinforce the controversy regarding the antagonistic roles of the two SPN populations. Indeed, optogenetic-mediated manipulations of D1R-SPNs and D2R-SPNs suggest that they can mediate “pro-rewarding” effects (47–52) or “aversion” depending on the type of manipulation (53), even though chemogenetic inhibition of D2R-SPNs leads to discrepant results (54,55). These studies highlight that D1R-SPNs and D2R-SPNs may rather act in a dynamic and concerted fashion

to control behavior. Accordingly, both populations are activated at the same time in the dorsolateral striatum during initiation of a reward-oriented action (49,56), which has been proposed to allow proper action sequence initiation (57). In addition to challenging the antagonism of both SPN populations, these findings call for caution regarding the interpretation of the results obtained by direct manipulations of SPNs on drug-related behaviors because they could result from perturbations of reward processing per se, rather than reflecting specific alterations of drug-induced behavioral adaptations.

In this context, Creed *et al.* (58) demonstrated that repeated cocaine exposure potentiates and depresses NAc D1R-SPN and D2R-SPN synapses, respectively, onto VP neurons. Optogenetically mediated depotentiation of D1R-SPN transmission onto the VP abolishes sensitized locomotor response, while potentiation of D2R-SPN-to-VP projections restores operant responding for sucrose in animals under cocaine withdrawal. These data suggest that D1R-SPN and D2R-SPN projections onto VP neurons mediate behavioral sensitization and cocaine-induced anhedonia, respectively (58). Yet, either chemogenetic activation of D1R-SPN or inhibition of D2R-SPN potentiates cocaine self-administration, which is reversed by chemogenetic inhibition of VP neurons (59).

Neurons specifically contacting each SPN subpopulation display distinct drug-induced structural plasticity, supporting input-specific alterations (60). In accordance, Luscher's group showed that cocaine-induced locomotor sensitization is associated with a potentiation of excitatory cortical inputs onto D1R-SPNs, but not D2R-SPNs, of the NAc (61). Optogenetically induced depotentiation of these synapses established the causality between drug-evoked plasticity in D1R-SPNs and behavioral sensitization (61). They also showed that mice trained to self-administer cocaine and subjected to a 30-day withdrawal display a potentiation of transmission at ventral hippocampal and cortical, but not amygdalar, excitatory projections onto NAc D1R-SPNs. Specific optogenetically induced patterns of stimulation decrease vigor response and abolish cocaine seeking when hippocampal and cortical inputs, respectively, are depotentiated (62). The same group also showed that compulsive self-stimulation of DA transmission, which models drug addiction, relies on the potentiation of excitatory projections from the orbitofrontal cortex onto D1R-SPNs of the ventrocentral striatum (63). These studies highlight that distinct components of drug addiction rely on drug-evoked synaptic adaptations at specific input projections onto D1R-SPNs. Accordingly, repeated cocaine exposure strengthens afferences from the basolateral amygdala onto D1R-SPNs but not D2R-SPNs (64). Inputs onto D2R-SPNs also seem to be altered by drug exposure because cocaine-induced CPP correlates with a strengthening of the coupling between hippocampal place cells and D2R-SPNs (65). However, further studies are necessary to establish causality between neurobiological adaptations onto D2R-SPNs and addictive behavior.

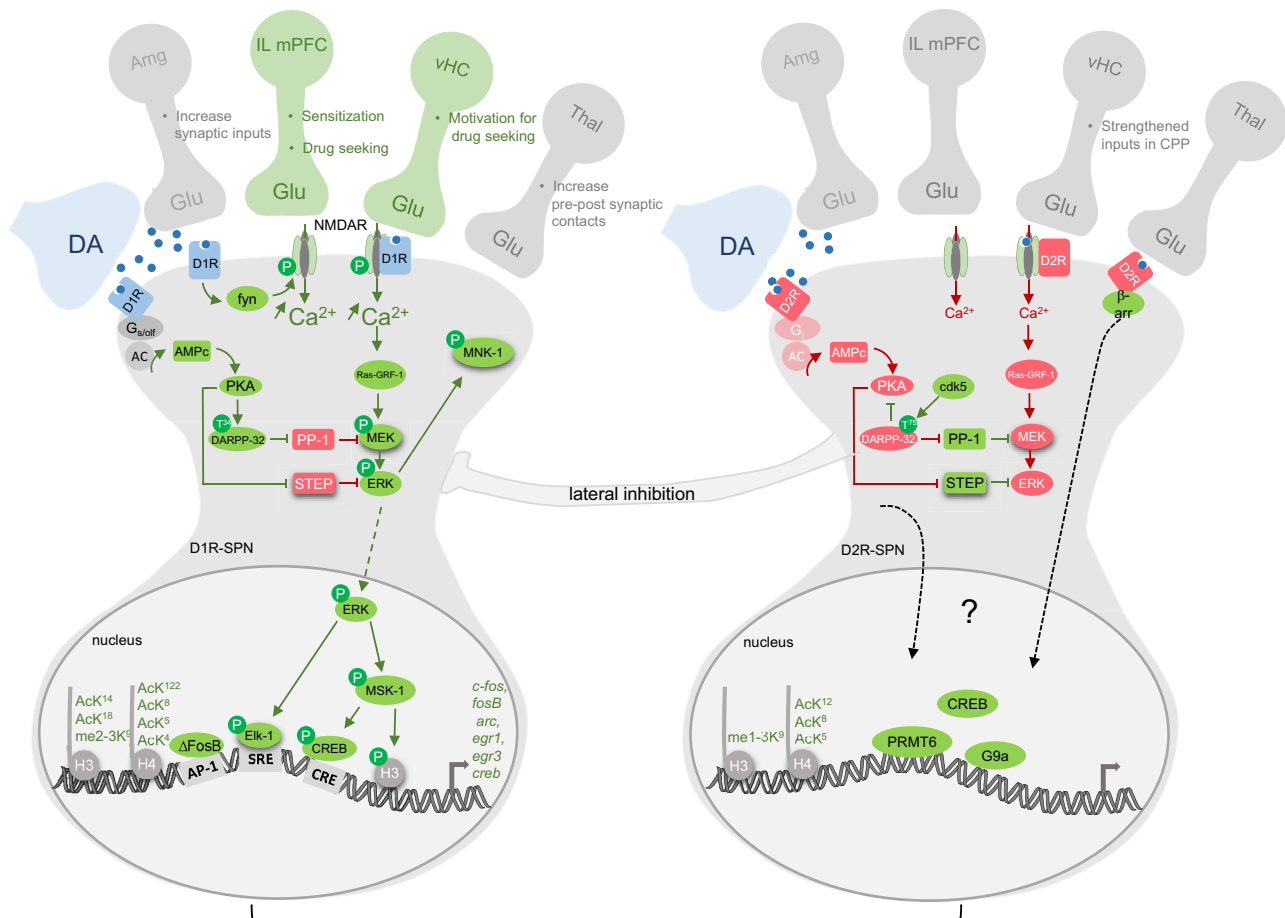
Beyond the comprehension of the mechanisms that underlie addiction, unraveling the precise alterations in synaptic connectivity between SPNs and input areas could inspire therapeutic strategies to reverse drug-induced synaptic changes, for instance through deep-brain or transcranial magnetic stimulation (66,67). Moreover, the identification of

specific drug-evoked synaptic changes highlights that addiction involves perturbation in the balance between glutamatergic inputs and DA modulatory signaling onto SPNs. This calls for a better understanding of the underlying molecular mechanisms as it may lead to identification of innovative molecular target (68).

### CELL-TYPE-SPECIFIC STRIATAL SIGNALING FROM THE MEMBRANE TOWARD THE NUCLEUS

Through differential coupling of DA receptors to  $G_{s/olf}$  and  $G_{i/o}$ , DA activates the cAMP (cyclic adenosine monophosphate)/downstream PKA (protein kinase A) pathway in D1R-SPNs, while repressing it in D2R-SPNs, leading to opposite regulations of ion channels, including glutamate receptors (69–71). The consensus is that DA increase facilitates glutamate-dependent activation of D1R-SPNs and inhibits glutamate-dependent activation of D2R-SPNs. Accordingly, acute cocaine administration triggers a fast  $D_1R$ -mediated  $Ca^{2+}$  increase in D1R-SPNs and a slow  $D_2R$ -dependent deactivation of D2R-SPNs in the DS of anesthetized mice (72). In freely moving mice, acute cocaine administration does not influence global neuronal activity in either subpopulation of the DS, although compact clusters of activity were identified in discrete subregions of the DS (73). Thus, cocaine-induced hyperlocomotion correlates with increased activity in D1R-SPN clusters near the dorsolateral striatum and a decrease in D2R-SPN clusters near the DMS (73). During cocaine-induced CPP, a transient  $Ca^{2+}$  rise occurs in NAc D1R-SPNs before entry in the drug-paired compartment, while  $Ca^{2+}$  decreases in D2R-SPN when the animal stays in this compartment (36). The mechanisms by which DA controls  $Ca^{2+}$  signaling were initially investigated through cell-specific overexpression in D1R-SPNs of NMDA glutamate receptor (NMDAR) bearing reduced  $Ca^{2+}$  permeability, which prevents the sensitizing and rewarding effects of cocaine (74), whereas the same manipulation in D2R-SPNs did not impact amphetamine-mediated CPP (75). NMDAR knockout in  $D_1R$ -expressing cells also blocks amphetamine-induced sensitization, a phenotype that is rescued by restoring functional NMDAR in NAc D1R-SPNs or deleting NMDAR in all SPNs (76). By contrast, NMDAR knockout in either  $D_1R$  cells or adenosine  $A_{2A}$  receptor ( $A_{2A}R$ ) cells (overlapping with D2R-SPNs), or both, preserves the development and extinction of cocaine-induced CPP (77). However, NMDAR deletion in  $D_1R$ , but not  $A_{2A}R$ , cells blunts CPP reinstatement, which is partially rescued by full NMDAR deletion (77). These findings highlight the critical role of a balanced NMDAR activity in each cell type for drug-induced responses. Although constitutive, and not striatal specific, these manipulations support a critical role of striatal DA and NMDAR signaling crosstalk in drug-evoked responses.

Downstream from these receptors, the ERK (extracellular signal-regulated kinase) pathway is activated by virtually all drugs of abuse (78). Global ERK inhibition blocks long-term potentiation of glutamate synapses impinging onto D1R-SPNs (61), cocaine-induced locomotor sensitization, and CPP (79,80) and the reconsolidation of drug-associated memories (81,82). Acute cocaine activates ERK in D1R-SPNs (24) via a mechanism that depends on both D1R and NMDAR (79,83). ERK activation thus behaves as a coincidence detector of



**Figure 1.** Cell-type-specific cellular and molecular events recruited from the plasma membrane to the nucleus in striatal projection neurons (SPNs) in response to psychostimulants. Diagram depicting major striatal signaling pathways and epigenetic and genic responses taking place from the membrane to the nucleus in (left) dopamine D<sub>1</sub> receptor (D1R)- or (right) D<sub>2</sub> receptor (D2R)-expressing SPNs in response to psychostimulants. Green and red arrows and lanes represent mechanisms described in the main text that are activated and inhibited, respectively, on dopamine release induced by psychostimulants. Glutamate afferences impinging onto each cell type are represented on top of each SPN subtype. Green afferences represent the ones for which a modulation of glutamate transmission induced by psychostimulants has been causally linked to distinct components of behavioral responses. Gray afferences represent the ones for which psychostimulant-induced changes in glutamate transmission have been either correlated to behavioral responses or not modified. AC, adenylate cyclase; AcK, acetyl-lysine; Amg, amygdala; AMPc, cyclic adenosine monophosphate; AP-1, activator protein-1; arc, activity-regulated cytoskeleton-associated protein; β-arr, β-arrestin; cdk5, cyclin-dependent kinase 5; CPP, conditioned place preference; CRE, calcium- and cyclic-AMP responsive element; CREB, cyclic adenosine monophosphate-responsive element binding protein; DA, dopamine; DARPP-32, dopamine and cyclic adenosine monophosphate-regulated phosphoprotein; egr1, early growth response 1; Elk-1, ETS-like-1 protein; ERK, extracellular signal-regulated kinase; Glu, glutamate; IL mPFC, infralimbic medial prefrontal cortex; me1-3K<sup>9</sup>, mono-, di-, tri-methyl-lysine 9; me2-3K<sup>9</sup>, di- tri-methyl-lysine 9; MEK, MAPKinase/ERK kinase; MNK-1, mitogen-activated protein kinase interacting protein-1; MSK-1, mitogen and stress-activated protein kinase-1; P, phosphorylation; PKA, protein kinase A; PP1, protein phosphatase 1; PRMT6, protein arginine methyltransferase 6; Ras-GRF-1, ras-guanine releasing factor-1; SRE, serum response element; STEP, striatal-enriched protein tyrosine phosphatase; T, threonine residue; Thal, thalamus; vHC, ventral hippocampus.

glutamate and DA signaling (84). This occurs through a cAMP-independent and D1R-mediated facilitation of GluN2B-containing NMDAR, triggering Ca<sup>2+</sup>-dependent ERK activation (83,85,86) (Figure 1). Nevertheless, inhibiting D<sub>1</sub>R-mediated potentiation of NMDAR targeting ERK activation in D1R-SPNs blocks the sensitizing and rewarding effects of cocaine (83). We also found that in NAc shell D1R-SPNs, acute cocaine triggers rapid de novo formation of dendritic spines contacting preexisting glutamate axon terminals (87). Stabilization of these newly formed synapses requires the targeting of the cytoplasmic MNK-1 (mitogen-activated protein kinase interacting protein-1) by ERK, which controls local translation

independently of nuclear events, and likely influences responses to subsequent drug exposure (87).

Downstream from D<sub>1</sub>R, the cAMP/PKA pathway also contributes to the facilitation of NMDAR functions by directly targeting specific subunits (88). Although PKA cannot directly target ERK, it can indirectly amplify its activation, notably via the cAMP-regulated phosphoprotein DARPP-32 [described in (85,86,89)]. Consistent with a D1R-SPN-specific ERK induction, cocaine increases DARPP-32 activity in D1R-SPNs and decreases it in D2R-SPNs (90). Deleting DARPP-32 in D1R-SPNs reduces basal locomotion and cocaine-induced hyperlocomotion, while its deletion in D2R-SPNs leads to an

opposite phenotype (91). Because DARPP-32 full knockout inhibits cocaine responses (89), cAMP/PKA/DARPP-32 signaling seems to prevail in D1R-SPNs over D2R-SPNs. Other possible pathways linking the D<sub>1</sub>R and cAMP/PKA pathways to ERK activation include the striatal-enriched protein phosphatase STEP, a phosphatase of ERK that is inhibited by PKA (85,89,92), and the neurotogenic cAMP sensor NCS-Rapgef2, for which ablation blocks cocaine-induced ERK activation in the NAc (93).

Despite the importance of the crosstalk between striatal DA and glutamate signaling for drug-induced adaptations, targeting of cognate receptors in humans to alleviate addiction led to a lack of efficacy and/or side effects over time (86), likely due to perturbation of crucial physiological functions. The development of biased ligands, recruiting specific pathways, opens the way toward the modulation of specific behavioral components (94). Little is known about their relevance in addiction, notably whether they could alleviate specific drug-evoked behavioral components while sparing nondrug reward processing. Interestingly, transgenic approaches show that biasing D<sub>2</sub>R toward arrestin signaling in the NAc affects cocaine-induced locomotion but not reward processing (95).

The physical interaction of DA receptors with other receptors also appears as a powerful mechanism by which receptors can mutually modify their functions through allosteric interactions resulting in functional selectivity. Hence, receptor heteromers are emerging as promising targets for fine-tuning of specific signaling pathways (96–98). One of the best-characterized receptor complexes is D<sub>2</sub>R–A<sub>2A</sub>R heteromers, which are detected in vivo in the striatum (99) and whose implication in reward and addiction is well reviewed (98,100). The key role of DA receptor–NMDAR interaction for their reciprocal modulation (101–104) makes these heteromers particularly relevant for addiction. Endogenous heteromers formed by D<sub>1</sub>R and the GluN1 NMDAR subunits are detected in the mouse striatum and act as a molecular bridge by which DA and glutamate exert their synergistic action on responses to cocaine in D1R-SPNs (105). Ex vivo electrophysiological recordings from D1R-SPN reporter mice show that the disruption of D<sub>1</sub>R/GluN1 interaction impedes D<sub>1</sub>R-mediated potentiation of NMDA postsynaptic currents; impedes long-term synaptic plasticity in D1R-SPNs, but not D2R-SPNs; and impedes cocaine-induced ERK activation (105). By contrast, D<sub>2</sub>R/GluN2B interaction mediates the inhibition of NMDA currents by DA in D2R-SPNs and alters the acute hyperlocomotor effect of cocaine (106). Hence, DA receptor/NMDAR heteromers may play a role in the imbalance between D1R-SPNs and D2R-SPNs induced by drugs of abuse, even though further work is needed to characterize their impact on downstream signaling toward the nucleus and long-lasting behavioral responses in vivo.

### GENETIC AND EPIGENETIC REGULATION

Like other forms of memory, addiction-related memories require changes in gene regulation and protein expression (107,108) taking place downstream from the activation of cytoplasm-to-nucleus signaling. Once activated in D1R-SPNs (24), ERK directly targets the transcription factor Elk-1 (ETS-like-1 protein) and indirectly the Ca<sup>2+</sup>-binding protein

and CREB (cAMP-responsive element binding protein) via the MSK-1 (mitogen and stress-activated protein kinase-1) (109–111). Cocaine-triggered Elk-1 phosphorylation downstream of D<sub>1</sub>R regulates the induction of immediate early genes (IEG), including *c-fos*, *zif268*, *Delta-fosB*, and *Arc* (110). As a consequence, inhibiting ERK-mediated Elk-1 phosphorylation blunts the sensitizing and rewarding effects of cocaine (110). By contrast, *Msk1*-deficient mice, which show altered histone H3 phosphorylation [a major cocaine-induced epigenetic mark in D1R-SPNs (24,111)], exhibit a downregulation of c-Fos and dynorphin expression, but not of *Zif268* expression, along with decreased locomotor sensitization but spared CPP (111).

The contribution of D1R-SPN-induced genes was initially established at the level of IEG through pharmacological studies and further confirmed using reporter mice (24,112). More comprehensive evidence came from the molecular profiling of FACS (fluorescence-activated cell sorting)-isolated c-Fos-positive neurons showing an enrichment of D1R-SPNs over D2R-SPN-specific genes, along with IEG (including *Arc* [activity-regulated cytoskeleton-associated protein] and *FosB*) in this cocaine-activated population (113). Functionally, D1R-SPN-specific knockout of *c-fos* alters cocaine-induced expression of neuronal plasticity-related gene, dendritic remodeling, and locomotor sensitization (114).  $\Delta$ FosB, the stable spliced version of *FosB* IEG, persistently accumulates in NAc D1R-SPNs after chronic psychostimulant exposure and plays a key role in cocaine addiction (107). This cell-type-specific  $\Delta$ FosB expression was further confirmed in reporter lines (115,116) or using ribosomal tagging approaches (117). On the other hand, D1R-SPN-specific overexpression of  $\Delta$ FosB led to increased silent synapses and immature spines formation (118), along with enhanced behavioral responses to cocaine and an increased sensitivity to this drug at low doses (118–120).

Psychostimulant exposure also affects IEG encoding effector proteins such as *Arc*, which is induced in the striatum downstream of D<sub>1</sub>R and ERK activation (121–123). Owing to its peculiar dendritic expression, the role of *Arc* in neuronal plasticity has been extensively described at synapses (124,125). However, acute cocaine induces an enrichment of *Arc* in the nucleus, where it colocalizes with active transcription regions and phosphorylated histones H3 (123). Consistently, *Arc*-deficient mice exhibit decreased chromatin compaction, higher RNA-polymerase II activity, and enhanced c-Fos expression, along with exacerbated cocaine-mediated CPP (123), revealing a homeostatic role of *Arc* in cocaine-induced gene expression. Other psychostimulant-regulated IEGs include genes encoding proteins involved in various cell functions, including mitochondrial or metabolic, which are differentially regulated in each SPN subpopulation after cocaine and play a key role in neuronal and behavioral adaptations to this drug (126–129).

Cell-type-specific genome-wide approaches, including FACS array profiling from D1R-SPN and D2R-SPN reporter lines (130) or cell-type-specific affinity purification of poly-somal messenger RNAs (117), revealed major differences in transcriptional landscapes between each subpopulation. A similar approach based on the use of Ribotag mice identified the transcription factor *Egr3* (early growth response 3) as

differentially regulated by chronic cocaine use in the two SPN subtypes with an increase in D1R-SPNs and a decrease in D2R-SPNs (131). Chromatin immunoprecipitation demonstrated the binding of *Egr3* to promoters of neuronal plasticity-associated genes *CamK2 $\alpha$*  (calcium/calmodulin-dependent protein kinase II $\alpha$ ) and CREB, which were further shown increased in D1R-SPNs and decreased in D2R-SPNs (131).

The persistent and experience-dependent features of addiction have suggested a role for epigenetic modifications, as they mediate stable transcriptional alterations supporting long-term remodeling of neuronal networks (4). Drugs affect multiple epigenetic processes including histone post-translational modifications, long-range chromatin reorganization, and noncoding RNAs (132).

Histone posttranslational modifications, including acetylation, methylation, or phosphorylation, gate DNA accessibility for transcription (133) and have been extensively studied in addiction (134). In particular, cocaine exposure induces a global increase in H3 and H4 acetylation (135–137), a transcription-permissive epigenetic mark (138). Chromatin immunoprecipitation-based analyses have been instrumental in understanding the contribution of these epigenetic changes to specific candidate gene regulation (132), as illustrated by H4 hyperacetylation at the *c-fos* promoter after acute, but not chronic, cocaine exposure (135). A genome-wide analysis of H3 and H4 pan-acetylation extended the mapping of cocaine-induced histone acetylation alterations at many genes predominantly induced in D1R-SPNs including *Arc*, *c-fos*, and *Egr3* (137). Direct assessment of cell-specific histone acetylation on FACS D1R-SPNs or D2R-SPNs (139) shows an increase in H3 and H4 acetylation in both populations after acute cocaine exposure, while H4 acetylation remain enriched only in D2R-SPNs after chronic exposure. This study also confirms the D1R-SPN-specific increase in Ser10-PH3 associated with *c-fos* transcriptional activation (140).

Histone lysine methylation is another cocaine-regulated modification that can either activate or repress transcription depending on the specific lysine (in this case, lysine K) residue targeted and its valence of methylation (141). In the NAc, chronic cocaine decreases the global level of dimethylation and trimethylation of H3K9 residue and downregulates its catalyzing enzymes, G9a histone methyltransferase (142). A ribosomal affinity purification approach shows that G9a expression is predominantly affected in D2R-SPNs in the whole striatum after cocaine exposure, and its specific knockdown in D2R-SPNs shifts these SPNs to a D1R-SPN phenotype, resulting in enhanced response to cocaine (143). NAc-specific profiling further demonstrates that the reduction of G9a specifically occurs in D1R-SPNs (131). Similarly, histone lysine methylation profile shows cell-specific regulations, depending on time and regimen of cocaine (139). Arginine methylation is decreased in D2R-SPNs together with downregulation of both PRMT6 (protein arginine methyltransferase 6) and its associated mark, asymmetric demethylation of R2 on histone H3 (H3R2me2a), after repeated exposure to cocaine (144). While direct methylation of DNA at specific promoter regions also plays a key role in gene regulation and cocaine-related behaviors (4), its cell-type specificity is yet unknown.

Growing evidence suggests a critical role for persistent changes in chromatin architecture in modulating subsequent neuronal responses during drug reexposure via a mechanism referred to as “gene priming.” This process could be involved in cell-type-specific long-term transcriptional alterations as recent observations show differential changes in chromatin accessibility between D1R-SPNs and D2R-SPNs after chronic cocaine exposure (145). Overall these data indicate that epigenetic remodeling could be critical in shaping the transcriptional program of D1R-SPNs and D2R-SPNs, although further investigations are now required to understand the cell-specific contribution of these processes.

Finally, much attention has been paid to microRNAs (miRNAs), a category of 21- to 25-nucleotides-long non-coding RNAs, which are altered in several psychiatric conditions (146), including addiction (147). miRNA, by repressing messenger RNA translation (148), are considered as “master regulators” of long-lasting transcriptional adaptations. miRNA-mediated gene regulation plays a role in cocaine-related changes in neurotransmission and behavior (148), but their cell-type-specific role in the striatum remains unknown. One study began to broadly address this issue by ablating a key protein in miRNA processing, Ago2, in D2R-SPNs (149). These mice showed loss of motivation to self-administer cocaine and a decrease of 23 (of 63) miRNAs induced by acute cocaine exposure. Questions as to whether and how miRNA regulation in D1R-SPNs occurs, along with the specific role of miRNAs in this neuronal population, remain to be answered.

## CONCLUSIONS AND PERSPECTIVES

While converging data point at a critical role for D1R-SPN-specific plasticity, cell-type-specific approaches reveal evident molecular alterations in D2R-SPNs in favor of their active role in the reshaping of striatal circuits in addiction. However, we still lack a comprehensive model for the contribution of intracellular pathways involved in drug-induced transcriptional alterations in D1R-SPNs and D2R-SPNs at various stages of addiction. Cell-type-specific approaches and timed-controlled interventions combined with genome-wide analysis of gene expression, epigenetic marks, and chromatin structure should deepen our understanding of the synergistic role of these two populations in drug-induced behavioral alterations. Establishing causality between drug-induced behavioral adaptations and discrete molecular and cellular mechanisms specific to each SPN population could allow the design of novel treatment strategies to alleviate selective behavioral components of addiction.

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## ARTICLE INFORMATION

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