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Opioid and psychostimulant plasticity: targeting overlap in nucleus accumbens glutamate signaling

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Abstract

Commonalities in addictive behavior, such as craving, stimuli-driven drug seeking, and a high propensity for relapse following abstinence, have pushed for a unified theory of addiction that encompasses most abused substances. This unitary theory has recently been challenged -- citing distinctions in structural neural plasticity, biochemical signaling, and neural circuitry to argue that addiction to opioids and psychostimulants are behaviorally and neurobiologically distinct. Recent more selective examination of drug-induced plasticity have highlighted that these two drug classes promote an overall reward circuitry signaling overlap through modifying excitatory synapses in the nucleus accumbens -- a key constituent of the reward system. We discuss adaptations in pre-/ postsynaptic, and extrasynaptic glutamate signaling produced by opioids and psychostimulants, and their relevance to circuit remodeling and addiction related behavior -- arguing that these core neural adaptations are important targets for developing pharmacotherapies to treat addiction to multiple drugs.

Keywords

addiction; opioids; psychostimulants; glutamate; nucleus accumbens; plasticity

Several decades of research have led to an understanding that addiction is a progressive pathology resulting from drug-induced neural plasticity within brain regions involved in reward, emotion, decision-making, and habit [1–3]. Commonalities in the ability of abused drugs such as opioids and psychostimulants to promote similar neurochemical,

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psychological (e.g., incubation of craving) and behavioral effects (e.g., sensitization, high propensity to relapse) have pushed for a unified theory of substance abuse. This view has recently been called into question, suggesting that addiction to psychostimulants and opioids differ at the behavioral, neurobiological, and even structural and circuit level [4–8]. The continued abuse of psychostimulants and recent rise in illicit opioid use, including opioid-based pain medications for non-therapeutic use [2, 9–14], has led to a need for more thorough examination of how much plasticity produced by these two drug classes overlap and diverge to better develop targeted therapies for addiction as a whole. The purpose of this review is to highlight recent work on glutamatergic transmission within the nucleus accumbens (NAc) -- a key neurobiological substrate of reward and motivated behavior -- using electrophysiological data from preclinical models. We contend that while psychostimulants and opioids do indeed exhibit important behavioral, biochemical, and physiological distinctions, as well as various dissimilarities in plasticity [15–17], they share a striking overlap in NAc glutamate plasticity at the presynaptic and postsynaptic level (Figure 1) that likely represents important focal points for development of future therapeutic strategies.

Psychostimulants and Opioids

Psychostimulants and opioids vary in chemical structure, pharmacodynamic profile, and physiological effects (Tanimoto coefficient < 0.85) [18, 19]. Despite these differences, these two drug classes do in fact share a number of core behavioral, neurochemical, and neurophysiological profiles. Behaviorally speaking, both drug classes promote motor sensitization, conditioned reward, drug-seeking and time-dependent increases in craving following extended periods of use [20, 21]. These parallels likely reflect overlapping neurotransmission and plasticity within shared circuits, although opioids do appear to involve more brain regions than psychostimulants with regards to relapse [7, 20, 22].

At the cellular and circuit level, psychostimulants produce similar effects on neuronal activity in the NAc [7, 20, 23]. This may reflect a shared ability to increase dopamine levels within the mesocorticolimbic dopamine system, albeit by different mechanisms. Psychostimulants do so by blocking reuptake (cocaine) or inverting dopamine transport (amphetamine), whereas opiates disinhibit DA neurons in the ventral tegmental area (VTA) through indirect inhibition of GABAergic input [24–26]. Notably, while it is well established that dopamine projections from the ventral tegmental area (VTA) to the NAc, data argue against a prominent role for dopamine in this circuit for opioid self-administration [7].

Preclinical Psychostimulant and Opioid Models

Numerous studies have examined effects of acute and repeated drug exposure using non-contingent models, whereby drug is administered via the experimenter with an intra-peritoneal or sub-cutaneous injection. These models include behavioral sensitization and conditioned place preference and can be used to measure rewarding/reinforcing properties of a drug, and drug-cue memories in their simplest form [7, 15, 20]. Unlike psychostimulants, the effects of non-contingent chronic opioid administration can also be studied through subcutaneous implantation of morphine pellets that promotes a steady state level of

morphine in the body. This approach permits examination of tolerance as well as dependence and withdrawal – the latter of which can occur spontaneously or be precipitated by opioid receptor antagonist administration [27]. Importantly, repeated and intermittent models often incorporate multiple 24 h periods of withdrawal, whereas steady dosing does not – an important consideration when interpreting neural adaptations produced by opioids. Complicating matters further, while physical signs associated with opioid withdrawal generally subside within a week, affective/cognitive components of withdrawal syndromes can persist upwards of 80 days [27, 28].

In volitional (contingent) drug administration models, animals learn to lever press (or nose poke) for intravenous infusion or oral administration of the drug, where responding on a specific lever results in drug delivery. An important finding is that in rodents and humans, there is a progressive intensification (“incubation”) of drug craving following the conclusion of cocaine or heroin self-administration [29–31]. In rodents, this is reported as an increase in lever responding (i.e., drug-seeking) in the absence of drug delivery, however while the incubating effects of cocaine are known to persist as long as 60 days, incubation seems to peak at ~15 d and return to control levels by 60 d following heroin self-administration [21].

NAC and medium spiny neurons

Drug-induced modifications in NAc glutamatergic neurotransmission has been identified as an underlying factor driving drug-taking, relapse, withdrawal and other drug-associated behavior for both drug classes [15–17]. The NAc is a heterogeneous structure that can be divided into core and shell region based on their anatomical connectivity and role in reward-related responses [32–34]. The NAc core is highly connected with motor circuitry and responsible for evaluation of reward and initializing reward-related motor activity [35–37]. Alternatively, the shell is highly connected with limbic and autonomic brain regions and is heavily involved in motivation and establishing learning associations [35, 38].

GABAergic medium-spiny projection neurons (MSNs) comprise a majority (>90%) of all neurons in the core and shell. MSNs receive coordinated input from glutamatergic afferents arising from several brain areas, including the basolateral amygdala (BLA), ventral hippocampus (vHPC), and medial prefrontal cortex (mPFC) [39]. Canonical understanding is that NAc medium spiny neurons (MSNs) can largely be divided into two sub-populations based on the expression of peptides, dopamine receptors (dopamine D1 vs. D2), and downstream projection targets [40–42], with a small fraction (~2–17%) expressing both D1- and D2-receptors [43, 44]. Unlike the distinct direct and indirect pathways of the dorsal striatum, information processing within the NAc and efferent regulation of basal ganglia output structures involves significantly more overlap between D1- and D2-MSN projections than previously believed [42, 44–46](12–16). Further, emerging evidence indicates that D1- and D2-MSN populations display different physiological characteristics, exhibit different forms of drug-induced plasticity, and generally exert antagonistic effects in drug-associated behaviors [42, 43, 47–49].

Psychostimulant and opioid effects on presynaptic glutamatergic release

Glutamatergic afferents in the NAc that collectively innervate single MSNs form a separate but unified system of information input [50]. This convergent neurotransmitter release promotes heterosynaptic plasticity and associative learning -- a common feature of addiction phenotypes [51–53] (see Figure 1 for presynaptic plasticity measurements). Examination of cocaine's effects on glutamate release at isolated inputs to MSNs, specifically the infralimbic cortex (ILC) and the paraventricular nucleus of the thalamus (PVNT), show an increase in the probability of release at early and late withdrawal time points [54, 55]. Cocaine-dependent increases in glutamate release appear restricted to ILC and PVNT afferents as no changes are observed at BLA or ventral hippocampal synapses onto D1- or D2-MSNs following experimenter administered cocaine [56]. As for opioids, glutamate release probability is elevated at BLA- but not prelimbic cortex (PrC)-to-MSNs projections in the NAc core as early as 2 hours following an escalating regimen of morphine over 5 days [57]. In the NAc shell, increased miniature excitatory postsynaptic current (mEPSC) frequency at D1-MSNs and reduced frequency at D2-MSNs accords with respective increases and decreases in release probability from pooled afferents 10–14 d after non-contingent morphine [47]. One likely possibility is that these changes may reflect modifications in prefrontal signaling, as repeated non-contingent morphine does not alter release at BLA or PVNT afferents[58].

Compared to the shell, direct evidence for withdrawal-dependent alterations in transmitter release in the NAc core is substantially lacking, however increased release probability has been observed at PrL-to-Core pooled MSNs following cocaine and remifentanyl self-administration, respectively [59, 60]. These are further substantiated by indirect evidence that cocaine-, heroin-, and morphine increase mEPSC frequency and/or suppresses presynaptic regulatory mechanisms such as metabotropic group II/III receptors (mGluR2/3R) and activator of G protein signaling (AGS3) at intermediate withdrawal periods [61, 62] [63–65] but see [66].

Although we lack an in-depth comparison of psychostimulant- or opioid-induced changes in presynaptic glutamate release based on withdrawal time points and mode of administration, the current data suggest that both drug classes collectively increase glutamate release on MSNs in the NAc, particularly at ILC afferents (Supplemental Table1) – begging the question whether tempering this release would be a beneficial therapeutic approach for treating drug addicted patients. To this end, clinical trials are identifying whether FDA approved medications believed to decrease glutamate release are potential therapeutic strategies for treating patients suffering from addiction. These medications are typically anti-seizure medications, such as zonisamide (tested to treat cocaine dependence), lamotrigine (tested to treat ketamine and alcohol dependence), and topiramate (tested to treat cocaine, alcohol, nicotine, or methamphetamine addictions) all believed to block varying types of voltage-gated sodium or calcium channel activity and in some cases, concomitant effects on glutamate transmission mediated by α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA)- and kainate-type receptors [67]. Although the mechanism is unclear, lamotrigine is believed to inhibit glutamate release from cortical-to-ventral striatal inputs making this medication potentially worth testing as a pharmacological treatment for patients

suffering from psychostimulant or opioid addiction [68]. Alternatively, agonists of putative autoreceptors and hetero-presynaptic mGluR2/3 receptors increase glutamate and dopamine release, a property that may position these drugs as potential treatment for dysphoria associated with early withdrawal [69]. The use of such anti-epileptics to dampen excitatory signaling still requires extensive preclinical testing of undesired side effects (i.e., fatigue, negative affect, depression) and examination of their ability to reverse drug-induced plasticity or produce plasticity on their own.

Extracellular (synaptic/perisynaptic) glutamate levels following psychostimulant or opioid exposure

Glial-dependent regulation of perisynaptic, extracellular glutamate strongly regulates synaptic plasticity through activation of extrasynaptic metabotropic glutamate and NMDA receptors [17, 70–72]. This regulation is primarily two-fold – occurring through the glutamate transporter, GLT-1, which is localized on glia in the vicinity of the synaptic cleft, and by release of glial-derived glutamate through the cystine-glutamate exchanger [59, 72, 73]. Both GLT-1 and the catalytic subunit of the exchanger (xCT) are downregulated after cocaine and heroin self-administration in the NAc core, as well as cocaine and morphine in the shell [17, 47, 74–79].

During withdrawal, downregulated xCT activity results in reduced glial-derived glutamate tone that normally activate presynaptic mGluR2/3 and postsynaptic mGluR5s that exert inhibitory tone on transmitter release. Effects of reduced presynaptic inhibitory tone are further exacerbated by drug-dependent reductions in GLT-1-dependent glutamate clearing [73, 80–82].

Electrophysiological and biochemical evidence suggests that re-exposure to drug and associated cues promotes rapid potentiation of glutamate transmission, and that this correlates with drug-seeking during reinstatement testing [59, 74, 83]. Although a direct causal link remains lacking, additional studies have shown that exposure to relapse-inducing stimuli following withdrawal from amphetamine, cocaine, and morphine, leads to a reduction in AMPAR signaling in the NAc shell and core [84–90]. These adaptations promote a scenario of uninhibited (potentiated) glutamate release triggered by re-exposure to drug or highly salient stimuli which may prolong postsynaptic signaling and synaptic spillover that perhaps represents and/or triggers a key form of short-term plasticity that closely shared by psychostimulants and opioids that is required to engage in drug-seeking behavior (i.e., reinstatement/relapse) [59, 60, 72, 74, 83, 91–95].

The above data suggest that proteins that regulate glial glutamate release and uptake may represent ideal targets for pharmacotherapies aimed at mitigating drug craving and relapse. A wide body of preclinical work supports this theory, as administration of either ceftriaxone (an antibiotic known to upregulate GLT-1 expression and function), or N-acetylcysteine (NAC; a prodrug that activates the exchanger) restores morphine, cocaine and heroin-induced pre- and postsynaptic plasticity, prevents stimuli-induced increases in glutamate release, blocks reinstatement of drug-seeking, and disrupts the rewarding properties of morphine [47, 59, 96]. However, bioavailability of NAC may limit its effectiveness in an

outpatient setting, while no known clinical trials have tested ceftriaxone efficacy as a treatment for addiction or assessed unintended side-effects in humans.

Psychostimulant and opioid-dependent generation of silent synapses

Silent synapses are excitatory glutamatergic synapses that express functional NMDARs, but lack functionally stable AMPARs [97]. They are formed either by synaptogenesis-like mechanisms or by silencing pre-existing synapses [98], thus acting as intermediary structures for strengthening or weakening glutamatergic synaptic inputs, respectively [99]. Contingent cocaine administration as well as non-contingent cocaine and morphine generate silent synapses in the NAc during early withdrawal. Interestingly, cocaine-generated silent synapses are preferentially expressed on D1R-MSNs [100, 101], whereas those generated by morphine exposure occur primarily on D2R-MSNs [100]. Following cocaine self-administration silent synapses have been observed in the shell at BLA- and ILC-to-Shell MSNs synapses and at PrL-to-MSNs in the core [102–104].

Mechanistic and temporal dynamics of silent synapses generation

Silent synapses are believed to represent key substrates for long-term neurocircuit alterations [105]. The conserved nature of silent synapse generation across drug classes suggests this may be a shared mechanism in facilitating circuit remodeling that initiates early stages of plasticity responsible for developing addictive behavior, however the mechanisms by which these synapses are generated appear to differ. Cocaine-induced synapse generation is associated with selective insertion of GluN2-containing NMDARs -- which are often expressed at newly developed synapses [102] -- increased dendritic spines [100, 106], and activation of the cAMP response element-binding protein (CREB), which promotes spinogenesis [106], suggesting that these are nascent synapses. On the other hand, exposure to morphine does not increase the synaptic expression of GluN2B-containing NMDARs, and increases the number of filopodia-like dendritic spines while decreasing thin-long spines [100]. As generation of these synapses is blocked by endocytosis-blocking peptides and AMPAR levels are correlated with spine head volume, morphine-induced generation of silent synapses is likely mediated by AMPAR removal at D2R-MSNs that ultimately weakens excitatory input to these neurons.

Despite these differences, a number of temporal and age-related similarities exist between cocaine and morphine silent synapses. First, both processes require repeated drug exposure, and is a gradual yet transient process that peaks at WD1-2 and returns to basal levels by WD7 [100, 102]. Second, although silent synapse development is normally more prominent during development (10%) vs. adulthood (~3%), both drugs produce large and comparable increases in silent synapses in middle-adolescent (~P35) and adults (~P65) in pooled MSNs (~25–30%) [102]. Lastly, when administered alongside conditioned cues silent synapse generation is increased in the NAc -- highlighting the possibility that this process may reflect a common mechanism for drug-associative learning [47, 107]. As exposure to relapse-inducing stimuli during withdrawal is sufficient to “restore” drug-induced increases in synaptic strength [85, 87, 90, 108, 109], it will be interesting to see if this plasticity is also associated with generation of silent synapses.

Overlapping neurocircuit reorganization in the NAc following psychostimulants or opioid treatment

Previous examination of structural plasticity in NAc MSNs showed that cocaine and amphetamine increases dendritic branching and spine density, while morphine had the opposite effect – causing long-lasting decreases in dendritic branching and number of spines [110]. Based on differential effects of opiates and psychostimulants on striatal immediate early gene (*Fos*) expression, it has been suggested that these opposing effects may be explained by engagement of direct versus indirect striatal pathways (i.e., D1R- vs. D2R-MSNs) [7]. This notion is supported by recent electrophysiological data in MSN subpopulations [100]. As withdrawal from cocaine progresses, newly generated synapses on D1R-MSNs are stabilized by the insertion of AMPARs [103, 104] precipitating stable, mushroom-like spines that enhance glutamatergic input at D1R-MSNs relative to D2R-MSNs [100]. Following repeated morphine treatment, the removal of AMPARs on preexisting D2R-MSN synapses generates “weakened”, transient spine structures that precipitates subsequent loss of dendritic spines and decreases in glutamatergic input on D2R-MSNs relative to D1R-MSNs [100]. Although easily interpreted as a major difference in drug effect, both these processes would likely produce a similar result in overall NAc circuitry (Figure 3) – that is a relative increase in excitatory drive on D1-MSN pathways responsible for promoting addiction-related behavior [47, 100, 106] [111].

Psychostimulant and opioid-dependent glutamate receptor plasticity

AMPA plasticity

Acute withdrawal—A wealth of data supports the notion that activation of and enduring adaptations in NAc AMPAR signaling plays a key role in psychostimulant- and opioid-dependent behavioral sensitization, conditioned reward, craving, and the continued propensity for relapse -- making these receptors a key target for studying how drugs of abuse promote persistent addicted behavior and guiding development of future pharmacotherapies [27, 47, 87, 95, 100, 112–118].

Although enduring changes in AMPAR signaling likely contribute to relapse, understanding the pharmacodynamic effects of early psychostimulant and opioid exposure may provide important insight into how drugs of abuse begin to co-opt the reward circuit and modify behavior. Electrophysiological characterization of AMPAR signaling using whole-cell recordings from pooled or separated populations of MSNs in the *NAc shell* suggested that neither acute cocaine or amphetamine, nor repeated cocaine or morphine, is sufficient to trigger changes in synaptic strength (A/N ratios; Figure 1, Box2) or the amplitude of AMPAR currents in the first 24 h when administered non-contingently [85, 119–123]. On the other hand, 24 h following the end of cocaine self-administration, mEPSC amplitude is reduced in recordings from pooled MSN [124]. This early adaptation may be important for future development of enhanced AMPAR signaling, as stimulation of D1R during early abstinence increased cocaine-induced reductions in AMPAR signaling, and prevented subsequent enhancement of synaptic strength [124]. In the *NAc core*, mEPSC amplitude and frequency, as well as GluA1 surface expression is elevated in pooled MSNs and tissue punches during early withdrawal from acute amphetamine and repeated cocaine, however

cocaine-dependent increases were only observed following 20–28 d (but not 7 d) of injections, the latter suggesting that extended exposure may promote significant un-silencing of synapses normally generated during early cocaine exposure [84, 102, 125].

Protracted withdrawal—Repeated non-contingent cocaine, amphetamine and morphine, as well as cocaine self-administration increased A/N ratios, basal AMPAR transmission (mEPSC amplitude and frequency), and expression of GluA2-lacking receptors in the NAc shell – an effect that occurs almost exclusively in D1R-MSNs [47, 53, 100, 121, 123, 125–127]. A single cocaine exposure has also been shown to upregulate NAc shell GluA2-lacking AMPAR signaling at D1R-MSN synapses, but like repeated exposure appears to require a period of withdrawal [127]. While non-contingent effects of cocaine on mEPSCs extend to the core in pooled MSNs, effects of repeated amphetamine (pooled MSNs) and morphine (identified MSNs) remain localized to the shell [47, 84].

Similar to non-contingent exposure, early biochemical and electrophysiological studies in pooled afferent and MSN populations showed elevated AMPAR signaling in the NAc core and shell following intermediate and long-term withdrawal (with or without extinction) from short- and long-access cocaine and heroin self-administration that was electrophysiologically shown to reflect a combination of GluA2-lacking and GluA2-containing receptors [81, 82, 85, 119, 124, 128–132]. These adaptations are almost exclusively isolated to D1R-MSN synapses in both the core and shell [53, 133] but see [127]. Although sufficient opioid self-administration data is lacking, these findings suggest that a core feature of opioid and stimulant exposure is a withdrawal-dependent progressive increase in NAc AMPAR signaling, regardless of exposure number and mode of drug administration (Figure 2).

Prefrontal-accumbens plasticity: NAc MSN excitatory synapses receive glutamatergic input from limbic and paralimbic regions -- each presumably contributing emotional and motivational information through variable forms of plasticity. The mPFC-to-NAc pathway has long been proposed to undergo drug-induced synaptic plasticity that is important for regulating opioid and psychostimulant relapse [8]. This pathway can be divided into two primary projections consisting of the ILC-to-Shell and PrC-to-Core projections. Optogenetic examination of these pathways has shown that ILC-to-Shell synapses are strengthened by increased insertion of GluA2-lacking receptors selectively at D1R-MSN synapses following withdrawal from non-contingent cocaine and morphine exposure (WD7–14), as well as short- and long-access cocaine self-administration (WD10–45) [47, 53, 104, 126, 127], but see [134]. PrC-to-Core synapses have been examined far less, however elevated AMPAR transmission in pooled MSNs following cocaine self-administration reflects insertion of canonical GluA2-containing AMPARs [104].

Allocortical-accumbens plasticity: Neighboring synapses in the NAc shell receiving input from the vHPC or BLA also display increased synaptic strength and AMPAR-EPSCs [53, 103, 127, 134]. Similar to PrL inputs, enhanced glutamate signaling at vHPC synapses appears to involve insertion of GluA2-containing AMPARs [53, 134]. While either non-contingent cocaine or morphine alter AMPAR transmission in pooled or identified MSNs [58, 134], data reporting effects on postsynaptic signaling within BLA projections appear to

be more susceptible to variations in model. Increases at BLA-to-Shell synapses likely reflect increased insertion of GluA2-lacking receptors on D2R-MSNs and perhaps GluA2-containing AMPARs in D1R-MSNs, as Pascoli *et al.* [53] examined rectification indices of AMPA transmission but not BLA-specific quantal transmission [53, 103, 127].

Behavioral and clinical relevance—Studies employing pharmacological and optogenetic manipulations suggest that restoration of opioid or psychostimulant-induced upregulation of NAc AMPARs exerts an inhibitory effect on opioid dependence/withdrawal, reward-seeking behavior, and a progressive intensification (“incubation”) of drug craving across [47, 58, 100, 103, 104, 122, 124, 128, 131, 135–137]. Several classes of AMPAR antagonists have undergone clinical trials for substance abuse treatment, including tezampanel (NGX424) and topiramate, which reduced cocaine self-administration (in rats), craving and increases the likelihood to remain abstinent from cocaine use which (humans) [114, 138–141].

Emerging evidence suggests that drugs that indirectly target AMPARs may provide an alternative approach, with fewer side-effects as direct effects. For example, positive allosteric modulators of AMPA receptors known as Ampakines, have been shown to alter psychostimulant behavior and modulate peptides that modulate drug seeking and glutamate plasticity (e.g., brain-derived neurotrophic factor, bdnf) [73]. Additionally, using synaptic stimulation patterns known to activate mGluR5s restores cocaine- and opioid-induced AMPAR signaling and disrupts relapse and conditioned reward across drug classes [47, 53, 76, 84, 126, 131, 142]. Although not addiction studies, ligands or compounds that modulate these receptors have been advanced to testing in clinical trials for various medical conditions and have some efficacy in alleviating somatic signs, anxiety and irritability associated with early opioid withdrawal in humans [143, 144]. Further examination of systemically available positive allosteric modulators of mGluR5 have shown favorable selectivity, side effect profiles, and anti-addiction properties [144–147].

NMDAR Plasticity

Numerous preclinical studies have illustrated the importance of NMDAR signaling in psychostimulant and opioid addiction pathology [59, 73, 148–150]. A majority of biochemical assessments during early withdrawal showed no change (many do not distinguish core and shell), with additional studies showing reductions in GluN1 or GluN2B expression -- the latter of which generally agrees with observed reductions in GluN-mediated EPSCs (core and shell were not distinguished here either) [81, 151–154].

More anatomically and physiologically discrete observations suggest a more likely scenario that involves a shift in subunit composition and/or localization of ‘detectable’ receptors (synaptic vs. extrasynaptic). For example, electrophysiological recordings in the NAc shell indicate that decay kinetics of GluN-mediated currents and sensitivity to GluN2B antagonists is increased 1–2 d following repeated non-contingent cocaine, which is accompanied by an increase in the cell surface levels of GluN1 and GluN2B subunits [100, 102, 106]. Alternatively, biochemical data show that total GluN2A (but not GluN2B) expression is upregulated in the NAc following chronic morphine, which matches with

observed NMDAR-mediated current decay kinetics [152, 155, 156] and a lack of altered sensitivity to ifenprodil following repeated morphine [100].

Corresponding increases in GluN1/GluN2B (and GluN2A) have been observed during early withdrawal from cocaine self-administration [157–159] but see [157–160]. Although upregulation of GluN2B expression in the shell did not equate to differences in the sensitivity of evoked synaptic currents to GluN2B antagonism, decay kinetics of spontaneous NMDAR-EPSCs were increased following blockade of glutamate reuptake, suggesting a diffusion of receptors to extrasynaptic locations that are inaccessible during synaptic recordings [159]. Whether opioid self-administration promotes similar changes in GluN2 subunits remains unclear, however this apparent divergence in subunit plasticity may reflect a unique role for GluN2A in opioid dependence/withdrawal (Box 3).

Protracted Withdrawal—Unlike acute withdrawal, protracted withdrawal appears to upregulate GluN2B (and/or GluN1) expression (core/shell total and surface) during intermediate withdrawal (7–21 d) regardless of drug class or mode of administration [104, 123, 130, 154, 161–163] [158, 160] but see [41, 129, 159]. Aligning with these findings, electrophysiological studies show an increase in GluN2B-mediated EPSCs in NAc shell and core following non-contingent morphine and self-administered heroin [81, 123, 164]. Thus, while increased GluN2B expression following cocaine promotes a continuum of GluN2B plasticity during early withdrawal [100, 102, 106], there appears to be a progressive shift in primary subunit composition from GluN2A to GluN2B during opioid withdrawal. However, caution is warranted, as data regarding subunit changes after prolonged withdrawal from chronic morphine, or acute withdrawal following intermittent morphine are lacking.

Functional and Clinical relevance of NMDAR plasticity—Pharmacological blockade of NMDARs, particularly those expressing the GluN2B subunit, inhibits opioid and psychostimulant conditioned reward [165–167] and drug-seeking [81, 168] -- effects that appear attributable in part, to activation of receptors in the NAc [164, 165, 169]. Given the conserved nature of increased GluN2B expression at silent synapses (cocaine) and intermediate withdrawal points across drug classes, it is tempting to speculate that upregulation of GluN2B in the NAc plays a key role in initiating or solidifying remodeling of NAc based reward circuits during withdrawal. Supporting this contention, increases in GluN1 and/or GluN2B are often paralleled by increases in GluA1 receptor expression [154, 160, 162, 163, 170], and cocaine-generated synapses that subsequently exhibit increased expression of AMPAR-mediated currents exhibit increased sensitivity to ifenprodil [100, 103, 104]. Moreover, systemic treatments that prevent drug-induced increases in GluN2B expression prevent increases in GluA1 expression, development or expression of sensitization [100, 103, 104, 154, 163, 170], and reinstatement of opioid conditioned reward and drug-seeking [81, 171]. However, although the subject of much debate, the notion that GluN2B-expressing receptors upregulates AMPARs seems to run counter to many studies indicating these sub-types exert a negative effect on AMPAR insertion/expression. How might this upregulation occur? One speculation is that it involves alterations extrasynaptic NMDAR-mediated regulation of slow-inward currents (SICs) or voltage-gated potassium channels due to a shift towards increased GluN2B:GluN2A-expressing receptors [81, 123,

172–174]. These changes may in turn promote increases in MSN intrinsic excitability that are known to precede and perhaps promote increased AMPAR signaling during withdrawal [123, 172, 173].

To date, clinical studies using NMDAR modulators have had relatively limited efficacy in the treatment of addiction, while partial agonists such as D-cycloserine may benefit extinction learning during cue exposure therapy [73, 175, 176], however the lack of consistency across trials indicate that additional studies are needed for these compounds. Alternatively, recent data indicate a need to develop and study novel ligands that weakly activate NMDARs, such as acamprosate, indirectly alter NMDAR function, or as the above data suggest, permit targeting of specific subpopulations of NMDARs based on subunit expression.

Concluding Remarks

Although the mechanism may differ across drug classes, the above data highlight a core feature of drug-induced plasticity at the circuit level -- a progressive increase in the ratio between excitatory synaptic drive at D1R- over D2R-MSN synapses during withdrawal (Figure 3). This shift in plasticity reflects a combination of presynaptic and postsynaptic changes that are not necessarily mutually exclusive. For example, withdrawal from cocaine and morphine promote increased glutamate release at D1R-MSNs, which is paralleled by a reduction in release at D2R-MSNs in morphine-treated mice [47, 54, 124, 125]. At the postsynaptic level, the development of cocaine-induced adaptations reflects generation of new silent synapses and concomitant spinogenesis preferentially on D1R-MSNs during early withdrawal that become stabilized with the progression of withdrawal through insertion of AMPARs in both the core and shell [100, 103, 104, 137]. Alternatively, during the early stages of withdrawal from repeated morphine administration, AMPARs are removed from synapses on D2-MSNs [100]. Over time, evidence suggests that these “weakened” glutamatergic synapses on D2R-MSNs are removed -- precipitating loss of dendritic spines and thus AMPAR-mediated glutamate transmission [47, 100]. While pathway-specific plasticity produced by cocaine and opioids varies, enhanced glutamatergic transmission within the PFC-to-NAc pathway is shared across drug classes and drug models [47, 53, 54, 126, 127], further reinforcing the importance of plasticity within this pathway in addiction.

Previous work identified opposing effects of psychostimulants and opioids on spine dynamics in NAc MSNs, suggesting that mechanisms underlying plasticity in these neurons is fundamentally different across drug classes. However, data from identified subpopulations of MSNs suggest that the overall effect of these microcircuit changes may be the same at macro level – increased excitatory drive at D1-MSNs. Comprising two parallel and distinct striatal pathways, activation of D1R- vs. D2R-MSNs appear to be diametrically opposed in their effects on behavior, with activation of D1R-MSN generally promoting behavior and reward and the D2R-MSN pathway more aligned with inhibition of behavior and aversion [66, 133, 177, 178]. Therefore, a shift in excitatory drive in favor of the D1R-MSN pathway may a critical modification that permits drugs of abuse to more readily control behavior during the development and persistence of addiction.

While the addiction field has made important leaps in understanding the neurobiological consequences of drug exposure and how these adaptations relate to addictive behavior, many issues need to be addressed going forward (Outstanding Questions). It is our hope that the above discussion has highlighted a number of important considerations going forward in the field of opioid and psychostimulant addiction research. Opioids and psychostimulants are known to promote plasticity across a number of brain regions which contribute to plasticity observed in the NAc and retain important implications for addiction in their own regard. Furthermore, these two drug classes undoubtedly produce distinct neurobiological, behavioral and psychological effects -- thus generalizations across drugs of abuse should be made with extreme caution [7]. However, these drugs also produce a number of similar adaptations, particularly changes in glutamate synaptic strength within the NAc, that when reversed by pharmacological or genetic means, disrupt reward and drug-seeking -- arguing that these adaptations are critical adaptations for treatments aimed at mitigating addiction to target (Figure 3, Key Figure).

Text Box 1: Nucleus accumbens glutamate receptors

AMPA Receptors—Of the three main families of glutamate-gated ion channels, AMPARs are the most dynamic – with receptor trafficking in and out of synapses contributing to changes in synaptic strength in many forms of plasticity [179]. Assembling as homo- or heterotetramers made up of GluA1-4, approximately 90% of GluA1 subunits in NAc MSNs are associated with GluA2 (GluA2-containing) creating receptors that are permeable to Na^+ but impermeable to Ca^{2+} and have a linear current-voltage (I–V) relationship [180, 181]. However, GluA1 expression is known to increase during experience-induced plasticity, which in turn favors formation of GluA1-homomeric AMPARs (GluA2-lacking) that are permeable to Ca^{2+} [182]. These GluA2-lacking receptors are permeable to Ca^{2+} [183] and correlate with enhanced channel conductance and long-term potentiation (LTP) leading to increased synaptic strength [181, 184].

NMDA Receptors—NMDA-type glutamate receptors (GluNs) often act in concert with co-localized AMPARs as synaptic coincidence detectors to facilitate plasticity [184]. Unlike AMPARs, NMDARs require glutamate binding and membrane depolarization to be activated. This depolarization expels extra extracellular Mg^{2+} from the channel pore, allowing Na^+ , K^+ , and Ca^{2+} to pass. Postsynaptic (or presynaptic) Ca^{2+} influx through NMDARs in turn activates intracellular signaling cascades that ultimately are responsible for changes in synaptic efficacy. NMDARs exist as heterotetramers composed of two obligatory GluN1 subunits, and two additional GluN2 or GluN3 subunits [184]. Differences in GluN2 subunit compositions (GluN2A–D) largely determines channel open time, intracellular coupling, and sometimes cellular localization. Most GluN1/GluN2A receptors are incorporated into synapses, while GluN1/GluN2B receptors are present at both synaptic and extrasynaptic sites [184]. Notably, evidence also suggests that expression of GluN subunits may be selective for MSN sub-populations, however data regarding this distribution is complex [185, 186].

Text Box 2: Measuring alterations in excitatory signaling

Modifications in transmission at excitatory synapses in the NAc often involve a combination of postsynaptic receptor and ion channel number/conductance [187], presynaptic neurotransmitter release, and glial-cell dependent regulation of non-synaptic extracellular glutamate [59, 73]. *Ex vivo* whole-cell patch clamp electrophysiology a very useful tool commonly used to assess these changes following exposure to drugs of abuse. Initial assessments of synaptic strength often begin by measuring synaptic AMPAR and NMDAR-mediated currents. This involves electrically or optically-evoking presynaptic glutamate release through axonal/terminal stimulation that binds to postsynaptic MSNs causing an influx of ions receptors that can be measured with a recording electrode as excitatory postsynaptic currents (EPSCs). Basal strength of excitatory synapses is difficult to compare between cells and acute slices using this approach due to variability in density of afferent fibers stimulated and number of synapses activated, thus responses are normalized isolating specific currents to construct a ratio of AMPAR:NMDAR currents that is independent of these variables. Importantly, by assessing AMPAR-mediated EPSCs at -80 mV and NMDAR-mediated currents at $+40$ mV, this method can circumvent the potential confound of changes in the proportion of Ca^{2+} -permeable AMPARs (GluA2-lacking) that would influence the AMPAR component when recorded at more depolarized ($+40$ mV) potentials.

Alterations in the A/N ratio, can reflect a change in AMPAR or NMDAR-mediated currents, making it important to ascertain the underlying mechanism. This can be done by examining post-synaptic responses to non-evoked release of neurotransmitter vesicles -- events that can be isolated as AMPAR- or NMDAR-dependent based on solution composition and voltage-clamp potential. Although terminology can vary, spontaneous EPSCs (sEPSCs) include action-potential-dependent and -independent currents, whereas miniature (mEPSCs) reflect events in the absence of action potentials -- thus corresponding to the response elicited by a single vesicle of transmitter [188].

Alterations in s/mEPSC amplitude is generally considered to reflect postsynaptic plasticity, whereas changes in frequency can be attributed to presynaptic release probability or transient postsynaptic modifications (increased receptor or synapse number) [105, 189]. To determine whether changes align with presynaptic modifications a paired pulse ratio (PPR) can be used to measure pre-synaptic efficacy [187]. Here, two EPSCs are evoked at varying inter-stimulus intervals (e.g., 20–200 ms), with the ratio defined as the amplitude of the second EPSC divided the first. Notably, discrepancies between mEPSCs and PPR should be interpreted with caution, as PPRs are generated from a limited number of stimulated synapses, whereas the mEPSCs reflect input from “all” afferents.

Text Box3: Potential targets for treating opioid dependence

Preclinical models of psychostimulant addiction often include non-contingent models (experimenter administration) to measure pharmacodynamic drug effects, rewarding/reinforcing properties of a drug, and drug-cue memories in their simplest form. Self-administration approaches on the other hand employ volitional drug intake where animals perform operant tasks (e.g., pressing a lever) to receive an intravenous infusion of drug. Following daily self-administration, animals typically undergo a period of forced-abstinence

(withdrawal) or extinction training, at which point re-exposure to the drug, drug-paired cue/contexts or stressors can be used to evoke renewed drug seeking.

Although not prevalent with psychostimulants, preclinical and clinical data indicate that following abrupt cessation of chronic or acute opioids can lead to precipitation of physical withdrawal and negative emotional states [27, 28, 135]. Preclinical approaches to examining tolerance and dependence often employ subcutaneous implantation of morphine pellets that promotes a steady state level of morphine in the body. Withdrawal can subsequently occur spontaneously or be precipitated by opioid receptor antagonist (Naloxone) administration [27]. This is drastically different from repeated intermittent non-contingent models that typically incorporate multiple 24 h periods of withdrawal throughout the experiment – an important consideration when interpreting neural adaptations produced by opioids. Complicating matters further, while physical signs of opioid withdrawal generally subside within a week, affective/cognitive components of withdrawal syndromes can persist upwards of 80 days [27, 28].

Manifestation of opioid-induced withdrawal signs align temporally with reductions in NAc core and shell GluA1 surface expression 1 or 72 h following repeated or acute morphine, respectively, while naloxone-precipitated withdrawal from chronic morphine is associated with reductions in NAc GluA2-lacking AMPARs [27, 100, 135, 190]. Alternatively, AMPAR-mediated signaling and surface expression is elevated in the NAc shell and core immediately (3–4 h) following an acute morphine injection (Anderson and Hearing, in press)[135], indicating that increases and decreases in AMPAR signaling may be important for the rewarding effects and withdrawal-associated aversive states, respectively. Biochemical and electrophysiological evidence also show time-dependent effects on NMDAR signaling whereby predominating GluN2A-expressing receptors during early withdrawal give-way to GluN2B-expressing receptors following more protracted withdrawal [100, 152, 156], suggesting a role for GluN2A receptors in development or expression of morphine tolerance or withdrawal, respectively. Supporting this contention, GluN2A knockout mice show marked loss of typical withdrawal abstinence behaviors precipitated by naloxone, which can be restored by rescuing GluN2A expression selectively in the NAc [191, 192]. These data highlight potentially unique adaptations produced by opioids during early withdrawal that may be early intervention targets for mitigating progressive increases drug use to avoid aversive effects associated with dependence and withdrawal.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Trends Box

- This review will provide an inimitable perspective on the striking overlap of neural adaptations in nucleus accumbens (NAc) excitatory produced by psychostimulants and opioids across preclinical and clinical data.
- We postulate that previously conceived notions of divergent plasticity may in fact have similar consequences at the behavioral and neural circuit level, and that neural adaptations that are *conserved* across multiple drug classes provide likely candidate mechanisms underlying core features of addiction and may provide more targetable mechanisms for future pharmacotherapies.
- Data discussed in this review will focus on electrophysiological (and to some extent biochemical) findings that touch on multiple forms of plasticity at NAc MSN glutamate synapses -- addressing what is known regarding the pharmacodynamic effects of psychostimulants and opioids from studies employing non-contingent models of drug administration, followed by examination of plasticity associated with intravenous drug self-administration and the relevance of these adaptations in preclinical models

Outstanding Questions

1. Do intrinsic differences in postsynaptic signaling mechanisms (e.g., receptor subunits, ion channels) permit drugs of abuse exert selective effects on specific sub-circuits of the NAc?
2. How do drugs of abuse selectively alter afferent specific plasticity within the NAc? Are their divergent forms of presynaptic regulation at sub-types of MSNs (e.g., mGluR2/3 versus eCBR)?
3. Do alterations in glial-dependent modulation of glutamate signaling differentially impact D1R-versus D2R-MSN signaling?
4. What are the temporal, subunit, cell-type, and pathway-specific adaptations in NAc NMDAR signaling following self-administration of psychostimulants versus opioids?
5. Do the apparent divergent effects of psychostimulants and opioids on MSN intrinsic excitability reflect cell-type specific differences and how does contribute to overall similar changes in NAc microcircuitry glutamate transmission discussed here?
6. While much is known about drug-induced plasticity in the NAc, what other brain regions (e.g., prefrontal cortex, ventral pallidum, basolateral amygdala, ventral tegmental area) exhibit overlapping and/or divergent forms of plasticity?

Figure 1. Measuring synaptic plasticity

Excitatory strength as measured by changes in the ratio of currents mediated by AMPA and NMDA-type (A/N ratio) glutamate receptors involves evoked stimulation of axon terminals by (a) injecting electrical current or (b) applying short pulses of light to evoke glutamate release from all surrounding terminals or specific afferents, respectively. (c) Following drug treatment, increases in mean A/N ratio may suggest an increase in GluA2-containing AMPA-type receptors (or reductions in NMDAR-mediated currents), while reductions in A/N ratios may reflect an increased presence of GluA2-lacking AMPA receptors that exhibit reduced current at more depolarized potentials (rectification). (d)

Alterations in transmitter release probability can be measured by comparing amplitudes of multiple EPSCs evoked electrically or optically (EPSC2/EPSC1). Reductions in paired pulse ratio (PPR) reflect an increase in release probability, while increases following treatment reflect a reduction. (e) Basal glutamate transmission is often measured by examining changes in the frequency or amplitude of EPSCs in the presence of TTX to eliminate activity-dependent transmission.

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Figure 2. Summary of known postsynaptic adaptations in glutamate receptor signaling and silent synapse expression following early and protracted withdrawal from psychostimulants or opioids Repeated exposure to psychostimulants and opioids promotes a number of overlapping postsynaptic modifications in excitatory postsynaptic currents mediated by the ionotropic AMPA- and NMDA-type receptors, as well as promote expression of silent synapses that express functional NMDA but not AMPA receptors (*silent*) on MSNs in the NAc shell (a, c) and core (b, d). These adaptations have been reported at synapses on D1R-MSNs (red), D2R-MSNs (green), and pooled populations of MSNs (tan), as well specific afferents arising from regions that include the paraventricular ventricular nucleus of the thalamus (PVT, pink), medial prefrontal cortex infralimbic (ILC, blue) and prelimbic (PrC, green) regions, basolateral amygdala (BLA, purple) and ventral hippocampus (orange). While anatomical, cellular, temporal, and mechanistic nuances certainly exist, known adaptations to data suggest that both drug classes increase silent synapse number during early withdrawal in both the core and shell, which are either stabilized or weakened as withdrawal becomes more protracted by subsequent insertion or removal of AMPARs that are permeable (GluA1/GluA1) or impermeable (GluA1/GluA2) to calcium.

Figure 3. Psychostimulants and opioids promote an overall increase in excitatory drive at NAc D1R-MSN pathways

Anatomical, pathway, model, and drug-specific differences in NAc plasticity certainly exist, however we propose a general (hypothetical model) based on current knowledge that these drugs have a similar overall effect on NAc circuitry. Both drug classes promote increases in silent synapse formation during early withdrawal. Psychostimulants (top) promote generation of new synapses on D1-MSNs that display increased GluN2B expression and subsequent insertion of GluA2-lacking or GluA2-containing (depending on the NAc subregion), while opioids (bottom) generate these on D2R-MSNs through endocytosis of AMPARs – resulting in increased excitatory strength at D1R-MSNs and reduced strength at

D2R-MSNs, respectively. It is possible that increases in presynaptic release observed as early as 24 h post drug exposure are initiated by reductions in inhibitory autoreceptor tone typically generated by the cysteine-glutamate exchanger, which in conjunction with reduced glutamate clearance from decreased GLT-1 expression, permit enhanced postsynaptic signaling that lead to maturation of D1R-MSN silent synapses. Although psychostimulants do not appear to alter pre- or postsynaptic plasticity at D2R-MSNs, opioids reduce both presynaptic and postsynaptic drive, the latter of which involves removal of AMPARs and ultimately synapse pruning. Based on this data, we posit that although the mechanisms by which overall changes occur may differ, both psychostimulants and opioids promote a progressive pathology with a similar net effect on NAc microcircuitry that promotes a relative (net) increase excitatory drive at D1R-MSNs that is likely important for drug-seeking and conditioned reward.

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