Published in final edited form as:
Curr Drug Abuse Rev. 2009 May ; 2(2): 195–213.

Phasic dopamine release in appetitive behaviors and drug abuse

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Abstract

Short phasic bursts of neuronal activity in dopamine neurons produce rapid and transient increases in extracellular dopamine concentrations throughout the mesocorticolimbic system, which are associated with the initiation of goal-directed behaviors. It is well established that acute exposure to many addictive drugs produce increases in tonic dopamine levels that occur on the order of minutes. However, recent studies suggest that abused drugs similarly enhance phasic dopamine release events that occur on a subsecond time scale. Furthermore, drug experience modulates the synaptic and intrinsic properties of dopamine neurons, which could affect dopamine burst firing and phasic dopamine release. This review will provide a general introduction to the mesolimbic dopamine system, as well as the primary methods used to detect dopamine neurons and dopamine release. We present the role of phasic dopamine release in appetitive behaviors in the context of contemporary theories regarding the function of dopamine. Next we discuss the known drug-induced changes to dopamine neurons and phasic release in both *in vitro* and *in vivo* preparations. Finally, we offer a simple model that chronic drug experience attenuates tonic/basal dopamine levels but promotes phasic dopamine release, which may result in aberrant goal-directed behaviors contributing to the development of addiction.

Keywords

dopamine; drug abuse; addiction; voltammetry

The dopamine system: anatomy and detection

The ventral tegmental area (VTA) and the neighboring substantia nigra (SN) are the primary dopamine producing nuclei in the brain [1]. The VTA is thought to play a particularly important role in drug abuse [2]. However, the SN has been studied far less in the context of drug abuse, with the majority of studies of this region focusing on its role in motor control [3]. A large proportion of the neurons whose cell bodies are in the VTA contain dopamine. For example, in the rat, 2/3 of the ~ 14,000 VTA neurons contain tyrosine hydroxylase, the rate-limiting enzyme in dopamine synthesis, and as such are presumably dopaminergic [1]. The non-dopamine producing cells in the VTA are likely GABA- and glutamate-producing; however, there is some debate whether glutamate and dopamine are co-released from the same neurons [4,5] or whether these neuronal subtypes exist in distinct populations [6]. The dopamine innervation from the VTA onto various nuclei depends upon the target, as dopamine neurons in the VTA comprise ~85% neurons projecting from VTA to the nucleus accumbens (NAcc), ~50% of the neurons projecting to the amygdala, and ~30% of the neurons to the prefrontal cortex (PFC) [1]. As with its projections, the VTA receives input from a diverse array of brain regions including the PFC, NAcc, bed nucleus of the stria terminalis, lateral dorsal tegmentum

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(LDT), pedunculopontine tegmental nucleus (PPT), amygdala and areas of the hypothalamus [7–10]. Thus, the VTA is a heterogeneous brain region with extensive afferent input and efferent projections.

In electrophysiological studies, dopamine neurons are identified *in vivo* primarily based on the presence of a triphasic and long-duration action potential waveform [11,12]. These neurons can (i) be hyperpolarized and quiescent, (ii) fire action potentials in a pacemaker-like fashion (2–10 Hz) or (iii) fire action potentials in bursts up to 15–30 Hz [11]. The pacemaker dopamine neuron firing is thought to give rise to the 'tonic' levels of dopamine with concentrations ranging from 5–20 nM [13,14], while the burst firing is thought to give rise to 'phasic' elevated dopamine levels which can reach as high as 1 μM [15,16]. The burst firing of dopamine neurons requires glutamatergic input, activation of N-methyl-D-aspartate (NMDA) receptors, opening of high-threshold calcium currents, and finally activation of calcium-activated potassium currents to terminate the burst [17]. Furthermore, activation of brainstem nuclei such as the PPT and LDT are involved in dopamine neuron burst generation [17,18] and dopamine release in the NAcc and striatum [9,19]. Although robust immunohistochemical methods can identify dopamine, GABA, and glutamate neurons in the VTA [6], electrophysiological identification of neuronal subtypes is problematic [20]. *In vivo* juxtacellular labeling of recorded VTA neurons in the rat demonstrate that many neurons with a triphasic and long-duration waveform actually are not dopaminergic [21], although it has been suggested that these findings are difficult to interpret because of methodological considerations [12].

In contrast to *in vivo* recordings, dopamine neurons in brain slice preparations do not spontaneously fire action potentials in bursts, but rather only exhibit pacemaker-like action potential firing [22]. The reported frequency of putative dopamine neuron firing in the slice varies whether one uses extracellular (3–8 Hz) [22], perforated-patch (2–5 Hz) [23], or whole-cell recordings (1–3 Hz) [20,24]. Regardless of the recording technique, the firing of putative GABA neurons is significantly greater than dopamine neurons and is usually higher than 10 Hz [22]. Although the firing rate can provide a crude segregation of neuronal subtypes in brain slices, a more reliable electrophysiological marker of dopamine neurons was found to be presence of the hyperpolarization-activated, cyclic nucleotide-regulated cation current (I_h) [22]. However, subsequent work found that not all cells with the I_h produced dopamine [20, 25], which may be explained by the species utilized, as the I_h is present in 98% of TH-containing neurons in the mouse VTA [24], but only in ~50% in the rat [20]. Recent studies highlight that the electrophysiological properties and pharmacological manipulations can identify dopamine neuron content in brain slices if the projection target of the neuron is known [26,27]. Regardless, many of the brain slice electrophysiological studies discussed below have solely used the I_h as a marker of dopamine content.

A number of analytical techniques are utilized to chemically detect dopamine *in vivo*. Some are best suited to detect tonic changes thought to arise from alterations in pacemaker-like firing, while others are optimized for isolating phasic dopamine release events thought to arise from burst firing [28–30]. One of the most commonly used methods is microdialysis, which has excellent selectivity and sensitivity for analyte detection; however, microdialysis suffers from relatively low temporal resolution (minutes) and is best suited for the quantitative analysis of basal and slowly changing tonic dopamine levels. In contrast, electrochemical techniques offer excellent temporal resolution to isolate phasic release events but offer poor analyte selectivity. These techniques take advantage of the fact that application of a modest potential (~200 mV vs Ag/AgCl) to a suitable electrode is sufficient to drive electrolysis of dopamine due to its oxidation to dopamine-*o*-quinone. The current produced by the electrolysis can be measured at the electrode and is proportional to the number of molecules undergoing oxidation, and therefore the concentration at the electrode surface. Different command waveforms can be used for the application of the potential to the electrode, the simplest being a continuous, constant

potential in (constant-potential) amperometry. This variant has microsecond temporal resolution and is often used to study the kinetics of dopamine release and reuptake; however, it offers little chemical selectivity since any oxidized compound will be detected with constant-potential amperometry recordings, which has deterred researchers from using this technique in behaving animals. A more selective electrochemical method is fast-scan cyclic voltammetry (FSCV), which utilizes a triangle input waveform to separate electrolysis from different analytes into temporally-resolved peaks in the output current. Since the voltage is swept to an oxidizing potential and back, current is generated (in opposite directions) during oxidation and reduction processes, whereby producing two electrochemical peaks for a given compound making chemical resolution more robust. FSCV can be employed to record dopamine release in awake-behaving rodents [28–30], and is capable of detecting changes in dopamine levels that occur in the range of 0.1 to 100 s [31].

The role of dopamine in appetitive behaviors: pharmacology, electrophysiology, and genetic techniques

Since the identification of dopamine over 50 years ago [32], a number of theories have been developed to explain the role of dopamine in behavior. We will briefly discuss some of the prominent theories and the supporting evidence to provide a framework for understanding the current views of dopamine function. We would like to preface that these theories are not necessarily mutually exclusive, but rather they provide different perspectives on the role of dopamine in behavior. More in depth discussion on theories of dopamine function can be found elsewhere [33–38].

The most well-established and uncontroversial theory of dopamine function is that dopamine release is involved with sensorimotor behaviors [33,35]. Dopamine plays a key role in motor tasks, as this is the primary deficit observed with those suffering from Parkinson's Disease (PD), a disease that leads to the selective degeneration of dopamine neurons [39]. However, it should be noted that symptoms of PD do not typically appear until a majority of SN dopamine neurons and terminals have degenerated [3,40]. Furthermore, mice that are deficient in dopamine production are catatonic and require supplements for survival and normal motor behaviors [41].

In addition to enabling normal motor activity, many lines of evidence support a critical role of dopamine in motivation [33,35]. For example, manipulations that impair dopamine signaling in the NAcc and are without effect on motor behavior have been found to shift food consumption from a preferred food option that required lever pressing for receipt toward a less palatable food option that was freely available [42–45]. In another behavioral assay that examined effort and motivation, rats were given an option in a T-maze to obtain a lower food reward with no obstacle or a higher food reward that required climbing over a barrier. Systemic dopamine receptor antagonism [46,47] or local dopamine depletions in the NAcc [48] shifted the response from the high reward side to the low reward side. Importantly, rats still preferred the high reward side when the barrier was removed under conditions when dopamine signaling was impaired, which suggests that these manipulations were not a result of a learning deficit [46–48]. Motivation is also assessed in operant tasks under progressive ratio (PR) reinforcement schedules. Under PR reinforcement paradigms, the operant requirement (the number of lever presses) increases on subsequent trials until the 'break-point', which is the number of lever presses for reinforcer delivery on the last completed trial and is a measure motivation [49]. Inhibiting dopamine signaling in the NAcc reduces the break-point for natural reinforcers [49–51]. Conversely, enhancing dopamine signaling in the NAcc by local amphetamine injections [52] or in mice with impaired dopamine transporter function [53] increases the break-point for natural reinforcers. Together, these studies highlight that

dopamine, especially within the NAcc, may function to overcome the motivational costs required for completing tasks requiring a high level of effort [35,54].

The 'incentive-salience' hypothesis of dopamine builds upon the general motivational hypothesis discussed above [33]. In short, incentive-salience is the neural representation of motivational value generated in response to a reward-related stimulus. This motivational representation is dynamic and can be applied to internally generated or externally experienced reward-related stimuli to give the stimulus incentive value, which can take control of behavior. In this hypothesis, it is thought that dopamine modulates the incentive value of such reward-related stimuli [33]. This hypothesis separates 'liking' of rewards, as measured by hedonic responses, from 'wanting' of the reward, as measured by motivational metrics [33]. Specifically, a variety of insults to the function of the dopamine system do not affect taste-reactivity or 'liking' [55–57]. Conversely, enhancing dopamine levels in dopamine transporter knock-down mice increases the 'wanting' for natural reinforcers as evidenced by increased break-points under PR reinforcement schedules [53] and by running faster to receive a reward [58]. These general findings have been mirrored in human studies where dopamine levels correspond to self-reports of 'wanting' and not to 'liking' [59,60].

Studies employing electrophysiological recordings of dopamine neurons in awake-behaving animals provide evidence that dopamine can encode a 'prediction-error' signal in the brain [37]. In primates and rats, it was found that dopamine neurons increase in firing to the receipt of a reward, but after training dopamine neurons instead fire to cues that predict the availability of the reward [61,62]. Interestingly, when a predicted reward is omitted, the firing of dopamine neurons is depressed [62]. Together, this evidence suggests that dopamine neuron firing signals the scalar discrepancy between the actual reward obtain and that predicted [62]. In support, dopamine neuron firing correlates with the probability of reward availability [63], as well as the magnitude of the reward [64]. Interestingly, the behavior of the phasic dopamine activation under these and other reward-related paradigms maps extraordinarily well onto a teaching signal proposed in the theoretical learning models in the field of reinforcement learning [38, 62,65]. However, some have argued that the phasic dopamine response in these tasks occurs too fast for any cortical-mediated computation to occur [34,66], suggesting that it contributes to a simple, low-computation process, consistent with (model-free) reinforcement learning models [67]. What becomes evident after examining these theories is that the dopamine system is associated with a diverse array of behaviors, which illustrates that dopamine may subserve various functions depending upon the location, context, and duration of its release [37]. Based upon the cellular effects of dopamine, it is thought that dopamine inhibits weak inputs and augments strong inputs to striatal neurons [68], which may also explain why dopamine is critically involved with many behaviors. The theories we have presented regarding the role of dopamine in behaviors was intended to provide a general framework for conceptualizing dopamine function. With this foundation, we will now explore the work that has specifically examined phasic dopamine release in the NAcc during appetitive behaviors.

The role of phasic dopamine release in appetitive behaviors: electrochemistry

The prominent theories of dopamine function developed primarily from the findings of pharmacological, genetic, and electrophysiological experimental techniques. However, these techniques do not provide direct information on dopamine release in forebrain terminal regions during discrete behavioral events on a physiological time scale. Pharmacological and genetic manipulations can produce long-lasting or permanent changes, which prevent using these techniques for isolating behavioral effects, related to dopamine changes, on a subsecond level. While electrophysiological recordings have excellent temporal resolution, it is not a perfect proxy of dopamine concentration since models of release processes incorporate several non-

linear functions [69]. Moreover, since there are currently no reliable electrophysiological criteria for sorting VTA neurons by their targets, these data cannot inform us on transmission in specific terminal structures. Therefore, voltammetric approaches, such as FSCV, offer an unparalleled capacity to quantitate phasic changes in dopamine concentration occurring on a physiological time scale. These techniques have provided further insights into dopamine's role in the brain during behavior that are complementary to pharmacological, genetic, and electrophysiological methods. Below we will discuss the findings regarding phasic dopamine release in the NAcc using FSCV in drug-free appetitive behaviors.

Presentation of novel sensory stimuli activates the mesocorticolimbic system. Specifically, electrophysiological recordings in both rats and primates indicate that putative dopamine neurons increase their firing rate in response to tactile stimulation [70], presentation of an auditory stimulus [70], or an unexpected delivery of sucrose [62]. In studies utilizing microdialysis, increases in dopamine overflow are observed after handling [71], and during sexual behaviors [72]. Using FSCV recordings in the NAcc, it was demonstrated that the number of spontaneous transient dopamine release events are enhanced six-fold in response to the presentation of a conspecific [73,74]. However, the effect on transient dopamine events was significantly attenuated with repeated conspecific presentations, presumably correlating with the reduced novelty and habituation towards the conspecific [73].

Although the frequency of dopamine transients increases during conspecific presentation, it is difficult to associate dopamine release to any one specific behavior [73]. Subsequent studies examined phasic dopamine release in response to more easily controlled experimental conditions, such as with the self-administration of sucrose [75]. Using FSCV it was found that dopamine levels increase in response to the presentation of a cue predicting sucrose availability, and that the peak in the rise of dopamine coincided with the lever press for sucrose [75]. Control experiments found that unreinforced cue presentations did not affect dopamine levels in naïve rats, suggesting that the phasic NAcc dopamine release observed in this task was dependent upon a learned association [75]. Further highlighting a role of phasic dopamine release in learned behaviors, FSCV recordings in the NAcc were made from rats undergoing Pavlovian conditioning where a conditioned stimulus (CS+) reliably predicts reinforcer delivery (unconditioned stimulus, US) [76–78]. Early in training, phasic dopamine responses are observed primarily to the reward retrieval (US). After rats learn the CS-US association, dopamine is released to the presentation of the (CS), while the response to the US is attenuated. However, a stimulus that did not predict reward availability (CS-) also increased dopamine release to the presentation and offset of the CS-, suggesting some generalization between the conditioned stimuli [76]. Together, these studies using a between-animal design suggest that there is a transfer of the phasic dopamine response from the US to the CS [76,77] that reflects the electrophysiological recordings in similar paradigms [36,61]. An important future FSCV experiment would be to utilize a within-animal design so that the time-course of the transfer from the US to the CS could be accurately determined. It should be noted that phasic dopamine release is observed to both the US and CS in rats [76], but dopamine neurons tend to fire only to either the US or the CS in primates [36]. This discrepancy could reflect differences in the species studies, the training paradigm utilized, or functional differences between dopamine neuron firing and release. It should be noted that despite the caveats raised above in relating *in vivo* electrophysiological data to dopamine release, all of these results in rats obtained using FSCV are extremely consistent with the electrophysiological studies performed in behaving monkeys and rats.

Some studies have examined the role of phasic dopamine release during intra-cranial self-stimulation (ICSS) procedures, where learning to lever press for a highly reinforcing electrical stimulation can be assessed within an animal in a single session [38,79]. A recent report found that the magnitude of dopamine released in the NAcc to cues predicting ICSS availability was

correlated with the learning to lever press for electrical stimulation [79]. Specifically, cue-evoked dopamine responses increased in magnitude during acquisition, disappeared during extinction, and reappeared upon reinstatement [79]. These results are exciting since they correlate dopamine responses with learning an operant task. Somewhat analogous to natural rewards, ICSS is dopamine-dependent [80], although maintained levels of dopamine release to the self-stimulation are not required for operant responding in ICSS paradigms [81]. However, caution should be exercised when extending these results to all aspects of natural reinforcerment because ICSS removes the sensory component of reward processing. To summarize, phasic dopamine release using FSCV has been assessed in many appetitive behaviors, and it is apparent that an increase in the number of phasic dopamine events in the NAcc is associated with novelty and unexpected rewards [73,74,76]. Experiments employing operant tasks also highlight that cues predicting reinforcer availability elevate dopamine release in the NAcc [75,79], where the peak dopamine response corresponds to the operant action [75,82]. Studies involving Pavlovian conditioning also suggest that phasic dopamine is released primarily to the US early in training and to the CS after extensive training [76,77]. Thus, these findings provide evidence of the involvement of phasic dopamine release in motor actions, motivation, modulating incentive value of reward-related stimuli, and learning. However, further experiments with multiple reward magnitudes will be required to determine if phasic dopamine release can also function as a prediction-error signal [36]. We will now discuss the effect of addictive drugs on the dopamine system, highlight how drugs alter phasic dopamine release, and suggest how these changes could modulate behavior.

The effect of abused substances on dopamine neurons: firing rate and tonic release

In order to understand the role of dopamine in drug abuse, it is important to first discuss how drugs affect the dopamine system acutely and after multiple drug exposures. Studies employing microdialysis techniques demonstrate that non-contingent administration of abused drugs such as alcohol, nicotine, opiates, psychostimulants, and cannabinoids increase dopamine levels in the NAcc [83,84], while non-habit forming drugs do not affect dopamine overflow [83]. The cellular mechanism by which addictive drugs increase dopamine levels depends upon the cellular targets of the drug studied. Psychostimulants such as amphetamine and cocaine enhance dopamine overflow by affecting dopamine clearance from the extracellular space [85,86]. Opiates activate dopamine neurons through inhibiting local GABA input [87,88]. Similar to opiates, ethanol reduces the firing of VTA GABA neurons [89], but also directly modulates the excitability of dopamine neurons [90–92]. Additionally, ethanol affects both excitatory and inhibitory neurotransmission in the VTA [93,94]. Nicotine activates and desensitizes dopamine neurons and inhibitory inputs to dopamine neurons in the VTA [95, 96], but prolonged nicotinic receptor activation is thought to cause a net excitatory effect on the dopamine system that may involve effects on presynaptic glutamate release [95,97]. Regardless of the cellular mechanism, *in vivo* and *in vitro* recordings of dopamine neurons demonstrate that non-contingent peripheral administration of alcohol [90], nicotine [96,98], opiates [87,88], and cannabinoids [99,100] increase dopamine neuron firing. Furthermore, nicotine [98], opiates [87], and cannabinoids [99] all increase the burst firing of dopamine neurons, which is thought to give rise to phasic dopamine release events [13]. Conversely, dopamine neuron firing is attenuated after administration of cocaine [101,102] and amphetamine [103] in anesthetized animals and brain slices, due to the autoinhibitory effects of dopamine at high concentrations after psychostimulant exposure [101].

While the acute effects of drugs are well studied, the effect of multiple drug exposures on the dopamine system is far more complicated in part because of differences arising from the drug studied, how the drug is administered (dose, frequency, and route), and the duration after drug experience. Although there is some debate, many studies support the notion that multiple drug

exposures lead to an impaired function of the dopamine system [104], though the timing of this effect can vary. For example, there is a transient (<10 days) increase in dopamine neuron activity in rats that received multiple non-contingent cocaine injections [105] or were trained to self-administer cocaine [106]. However, multiple non-contingent cocaine injections decrease dopamine neuron population activity after 3–5 wks of withdrawal [107], and also reduce dopamine overflow starting 24 hrs after the last drug exposure and last for at least 10 days [108–110]. Similar to extended withdrawal after chronic cocaine treatment, the activity of dopamine neurons and tonic/basal dopamine levels are reduced after chronic treatment of amphetamine [110], nicotine [107,111], ethanol [107,110,112,113], and morphine [110,114, 115], but see [116]. Interestingly, chronic treatment with cannabinoids attenuated basal burst firing and the cannabinoid-mediated increase in firing rates in SN dopamine neurons, but was without effect on VTA dopamine neurons [117]. A subsequent drug exposure after withdrawal from chronic drug experience has been shown to return dopamine neuron firing rates and dopamine release to and above basal levels with ethanol [118], amphetamine [119], and morphine [114], but see [116]. Collectively, these studies suggest that drugs acutely active the dopamine system, but chronic drug exposure dampens basal/tonic dopamine levels.

The effect of abused substances on dopamine neurons: synaptic plasticity and burst firing

As discussed above, dopamine burst firing requires glutamatergic input, NMDA receptor activation, opening of high-threshold calcium currents, and finally activation of calcium-activated potassium currents to terminate the burst [17]. Thus, it follows that changes in synaptic inputs, calcium currents, or calcium-activated potassium currents could alter burst patterns of firing in dopamine neurons. Although incomplete, a growing body of evidence suggests that abused drugs can modify the synaptic inputs onto dopamine neurons as well as the currents found in dopamine neurons important for burst generation. For example, many studies have now shown that a single non-contingent injection of cocaine increases the ratio of a-amino-3-hydroxy-5-methylisoxazole-4-propionic acid (AMPA) receptor currents to NMDA receptor currents (AMPA/NMDA) on VTA dopamine neurons [120–125]. This effect is observed 24 hours after the cocaine injection, and persists for up to 5 days [124]. The AMPA/NMDA ratio is thought to be a reliable measure of excitatory synaptic strength, where increases have been associated with enhanced AMPA receptor function [120,124,126]. In agreement with enhanced excitatory synaptic function on dopamine neurons, a single cocaine injection also increased the frequency and amplitude of miniature excitatory post-synaptic currents [124]. Furthermore, increases in the AMPA/NMDA ratio are associated with an impaired ability to generate long-term potentiation (LTP), a cellular mechanism that strengthens excitatory synapses and is thought to be important in learning and memory [124,127]. Thus, an enhanced AMPA/NMDA ratio is likely occluding the ability to elicit LTP because the excitatory synapse cannot be further strengthened [124,127]. However, for the purpose of this discussion, we highlight that such augmentations in the AMPA/NMDA ratio are enhancing excitatory synaptic strength that could promote burst generation in dopamine neurons.

While much of the work examining synaptic alterations on dopamine neurons has focused on the effects of cocaine, similar increases in the AMPA/NMDA ratio on VTA dopamine neurons have been observed 24 hrs after a single injection of amphetamine, nicotine, or morphine [123]. Subsequent work demonstrated that these synaptic changes are rapid, as an enhanced AMPA/NMDA ratio is observed 2–3 hrs after injection of cocaine and amphetamine [128, 129]. Interestingly, *in vitro* exposure to cocaine transiently increases NMDA receptor currents [130] and increases the AMPA/NMDA ratio after 3–5 hrs [128], although this may not extend to all psychostimulants [129].

Many studies examining drug-mediated changes on VTA dopamine neuron synaptic plasticity utilized non-contingent drug-administration, though recent studies have now examined these synaptic changes under conditions where rodents self-administer the drug. For example, an increase in VTA AMPA receptor levels is observed in rats that have self-administered nicotine [131]. Interestingly, food, sucrose, and cocaine self-administration increase the AMPA/NMDA ratio immediately after training, but only rats that self-administered cocaine (and not yoked controls) exhibited a persistent increase in the AMPA/NMDA ratio [132]. This study highlights how the changes on VTA dopamine neurons will depend upon the method of drug administration, as chronic peripheral injection of cocaine transiently (< 10 days) affects the AMPA/NMDA ratio [121], though these changes are longer lasting (> 21 days) in self-administering rodents [132]. Originally, it was hypothesized that these changes in glutamate receptor function are responsible for behavioral sensitization, which is an enhanced motor response to a subsequent drug exposure) [124]. Instead, further studies found that the AMPA/NMDA ratio is not associated with the development of behavioral sensitization [121,125], but rather may be important for initiating long-lasting changes, which promote addiction-like behaviors [132,133].

Recently, addictive drugs have been shown to affect inhibitory synaptic inputs on VTA dopamine neurons. Multiple injections of cocaine [122] and a single injection of morphine [134] reduce the inhibitory input on VTA dopamine neurons. These effects are not unitary across drugs, as a single injection of ethanol was found to increase inhibitory input on VTA dopamine neurons [135]. However, withdrawal after chronic ethanol exposure promotes burst firing of dopamine neurons by inhibiting the function of calcium-activated potassium currents [136]. These studies highlight that exposure to addictive substances can strengthen excitatory synaptic input, reduce inhibitory synaptic input, and alter the function of ion currents in VTA dopamine neurons. While these drug-induced adaptations have not been characterized or identified for all addictive substances, we suggest that these changes will increase the burst firing of VTA dopamine neurons, since this firing pattern is dependent upon glutamatergic input, NMDA receptor activation, and calcium-activated potassium currents [17]. In support, dopamine burst firing is elevated in an anesthetized preparation using rats that readily self-administer cocaine [137], or in rats during early withdrawal after cocaine self-administration [106]. We therefore would expect that behaviorally relevant stimuli would enhance dopamine burst firing to a greater level after experience with drugs. Empirical data of dopamine neuron firing patterns in awake-behaving rodents after drug exposure is lacking, though recent studies have begun to examine these questions by examining phasic dopamine release, thought to be dependent upon burst firing [13], with FSCV in rodents during drug-related behaviors.

The effect of abused substances on phasic dopamine release

FSCV has been utilized to examine phasic dopamine release in a variety of model systems, though it is important to note that drug-mediated effects on dopamine release can result from direct effects on dopamine neuron excitability or from changes in dopamine uptake. Numerous studies have examined the effect of ethanol on dopamine release in striatal brain slices from drug-naïve rats, and it was shown that moderate doses were without effect on dopamine uptake [138–140]. In contrast, chronic ethanol vapor exposed rats exhibited enhanced dopamine uptake *in vitro*, which was thought to be a compensatory mechanism resulting from the elevated dopamine levels due to the prolonged ethanol treatment [141]. In awake, behaving rodents, acute peripheral injections of ethanol at doses that increase tonic dopamine neuron firing were found to attenuate electrically stimulated dopamine release [142]. This ethanol-mediated reduction of phasic dopamine release was thought to result from enhanced tonic dopamine levels that impaired phasic dopamine release due to depletion of releasable dopamine and activation of release-regulating autoreceptors [142]. However, intravenous ethanol infusions sometimes increased the frequency of spontaneous phasic dopamine transients in awake-

behaving rats [143]. Similar effects have also been observed with cannabinoid receptor activation, where intravenous infusions of cannabinoids reduced electrically stimulated dopamine release, but increased the frequency and amplitude of spontaneous phasic dopamine release events [144]. These findings with ethanol and cannabinoid administration highlight that it can be difficult to parsimoniously use the findings from *in vitro* preparations and artificial electrical stimulations to predict the net effect in awake, behaving rodents. Reductionalist preparations and electrical stimulations are better suited to examine specific aspects of dopamine transmission, such as the involvement of specific ion channels, changes in release kinetics and the quantity of dopamine release, which can more difficult to accurately ascertain using *in vivo* preparations. Regardless, these findings highlight that ethanol and cannabinoids produce changes in phasic dopamine release.

A number of studies have examined the effect of nicotine on phasic dopamine release in both *in vitro* and *in vivo* preparations. In contrast to ethanol, acute *in vivo* nicotine exposure enhances dopamine uptake in the striatum [145]. Nicotine exerts frequency-dependent effects on phasically stimulated dopamine release *in vitro*, where at low firing rates dopamine release is attenuated, but at high firing bursts nicotine enhances dopamine release [146,147]. Intravenous infusions of nicotine were also found to increase the frequency and amplitude of spontaneous phasic dopamine release events [143]. In agreement with the findings from other abused substances, intravenous infusions of cocaine also increase spontaneous phasic dopamine release events in the NAcc [31,143,148–150]. Interestingly, endogenous cannabinoids modulate the cocaine-, nicotine-, and ethanol-mediated increases in phasic dopamine release, as the effects of drugs on phasic dopamine release are attenuated by systemic cannabinoid receptor antagonism [143]. While the locus of this effect is yet to be determined, it is speculated that it is within the VTA, where cannabinoid receptor activation reduces GABA release on VTA dopamine neurons [151]. Together, these findings suggest that abused drugs may exert similar effects on phasic dopamine release even though their respective cellular effects are quite distinct. Future studies are required to systematically examine drug-specific effects on phasic dopamine release. Below we discuss the effects of cocaine on phasic dopamine release, as this has been the most thoroughly studied addictive substance.

Early microdialysis studies found that abused drugs have regionally distinct effects on tonic dopamine levels with the greatest enhancement of dopamine levels found in the ventral striatum [83,84]. A recent report identified regional differences on cocaine-mediated effects on phasic dopamine release with larger effects in the NAcc shell subregion compared to the NAcc core [148]. It was suggested that the preferential effect on dopamine release in the NAcc shell by cocaine could be critically important for the primary reinforcing effects of drug [148]. Similar to differential effects of contingent and non-contingent drug administration on synaptic plasticity on VTA dopamine neurons [132], the effect of cocaine infusions on phasic dopamine release can depend upon the contingency of the administration [149]. No changes in dopamine levels are observed within 10 s of a non-contingent cocaine administration to awake, drug-naïve rats. However, phasic dopamine events are increased during this time frame with contingent cocaine administration, highlighting that these early dopamine release events (< 10 s after drug delivery) may be important for learned associations, and are not a result of the pharmacological actions of cocaine [149]. Identical to natural reinforcers [75,79], cues that predict cocaine availability are able to elicit phasic dopamine release that persist even when the drug is not administered [150,152]. Interestingly, the rise in dopamine levels is associated with the initiation of approach to lever press for cocaine [149,150,152], which is thought to be causal since stimulation of dopamine neurons was found to promote this behavior [152]. The field of FSCV recordings in behaving rodents during drug-related behaviors is nascent, and many questions regarding the prolonged effects on drugs on phasic dopamine release remain unanswered. One limitation present in many behavioral studies using FSCV arises from the usage of acute glass-insulated microelectrodes, which need to be physically inserted on each

recording day. Due to this approach with acute recordings, FSCV recordings are likely in different locations across days, and successfully inserting electrodes becomes more difficult after multiple recordings sessions [30]. We have developed chronically implanted microelectrodes that permits for stable FSCV recordings over multiple days and is well-suited to address changes in phasic dopamine release over long-lasting behavioral paradigms (manuscript in preparation). Future studies employing chronically implanted FSCV electrodes will be able to test for changes in the pattern of phasic dopamine release during the transition to compulsive drug taking in rodent models of addiction.

Mesocorticolimbic function in human addicts

The development of human imaging techniques has provided insights into functional changes within the brain that occur in human addicts, which support many of the effects observed in rodents. Many human addiction studies have utilized functional magnetic resonance imaging (fMRI) or positron emission tomography (PET) [153]; however, it is important to note that the fMRI and PET identify changes on the order of seconds to minutes, while FSCV can identify phasic dopamine changes on a subsecond time scale in rodents [28,154]. fMRI identifies changes in blood oxygen levels, with a time resolution of a few seconds, thought to represent changes in neural activity. PET can be used to make more specific measurements of neurotransmission by monitoring radiotracers that selectively bind to proteins. For example, radiolabeled dopamine-receptor ligands can be monitored in the brain, and their concentration decreases as they are displaced from receptors following release of endogenous dopamine. However, the temporal resolution for PET is in minutes and only increases, not decreases, in dopamine concentration are detected [155].

Only recently with fMRI was it shown that the VTA is activated by rewarding events in humans [156], which mirrors the electrophysiological recordings of dopamine neurons from primates and rodents [61,62]. Paralleling rodent work [83], exposure to psychostimulants increased dopamine levels in the human striatum that was associated with the reinforcing effects of the drug [157–159]. Furthermore, decreased striatal dopamine responses were reported in detoxified cocaine abusers [160], consistent with the lower dopamine population activity and dopamine overflow in rodents after chronic drug exposure [107–110]. The level of radiolabeled dopamine-receptor ligands under basal conditions has also proved useful in assessing difference in neural function between individuals. Human abusers of alcohol [161], cocaine [162], heroin [163], and methamphetamine [164] have lower levels of dopamine receptor binding compared to non-abusers, which has led to the hypothesis that low numbers of dopamine receptors, whether due to genetics or previous drug exposure, can make an individual more susceptible to drug abuse [153–155]. Moreover, individuals that are resistant to drug use (close relatives of addicts that do not abuse drugs) exhibit increased dopamine receptor binding, suggesting that higher levels of dopamine receptors could protect against the development of addiction [165]. While alterations in the level of radiotracer binding may reflect changes in receptor affinity rather than actual receptor number, this metric is incredibly robust, indicating important underlying physiological differences. In summary, human imaging studies have provided evidence that drugs acutely increase dopamine levels and that chronic drug exposure impairs the function of the dopamine system; however, improving the temporal resolution in current imaging techniques will allow for a more direct examination of phasic dopamine signals in addicts.

The role of phasic dopamine release in drug abuse

Briefly, we will summarize what we have discussed in this review and offer our model regarding the role of phasic dopamine release in the development of drug abuse, which is also schematically presented in Fig. (1). Dopamine neurons can fire in a regular pacemaker-like

fashion, which is thought to give rise to the tonic levels of dopamine [13,14]. Alternatively, dopamine neurons can fire in bursts, which is thought to produce phasic dopamine release events [15,16]. In a drug-naïve state there will be a tonic dopamine tone arising from pacemaker-like dopamine neuron firing. Behaviorally-relevant novel stimuli will increase dopamine burst firing [70] and phasic dopamine release [73]. However, presentation of stimuli associated with drug intake, such as drug paraphernalia or cues predicting drug availability, will not affect dopamine neuron firing or release because these stimuli are not salient in a drug-naïve state.

After an association is learned between a reinforcer and a cue predicting reinforcer availability, the cue in turn becomes salient and can elicit phasic dopamine release for natural [75,76,79], and drug reinforcers [149]. Interestingly, cues predicting drug availability appear to be more resistant to extinction than cues predicting non-drug reinforcer availability [79,150], which suggests that additional changes occur in the dopamine system due to the drug experience. In support, learning an association between cues and natural reinforcers transiently affects the synaptic properties of dopamine neurons [78,132], while drug experience promotes long-lasting changes to the intrinsic and synaptic properties of dopamine neurons [124,132,136]. We posit that these prolonged cellular adaptations in dopamine neurons after drug experience will function to strengthen previously learned associations and promote dopamine burst firing and phasic release in response to previously weak or neutral stimuli. In addition, withdrawal after chronic drug exposure attenuates tonic dopamine levels and dopamine neuron population activity [107–115]. Together, this suggests that chronic drug exposure will enhance the ‘signal to noise’ of phasic dopamine release events, where the phasic ‘signals’ become more salient due to the attenuated ‘noise’ of tonic background dopamine levels. Because phasic dopamine release is associated with initiating goal-directed behaviors [75,149,152], it follows that the enhanced ‘signal to noise’ of phasic dopamine signaling will promote drug seeking in response to drug-related stimuli, which is important in the development of addiction. A corollary of this hypothesis is that chronic drug exposure will also affect the processing of cue-related associations that do not involve drugs. In support, amphetamine treatment promotes habit formation after reinforcer devaluation [166], and enhances both inhibitory and excitatory Pavlovian associations [167,168]. Furthermore, human addicts and healthy subjects with reduced dopaminergic function exhibit impaired decision-making abilities [169–171], highlighting that dysregulation of the dopamine system can alter cognition and behavior. Therefore, addiction can be debilitating for individuals because chronic drug experience not only promotes drug seeking, but also affects proper decision-making.

Others have suggested that dysfunctions in the dopamine system are involved with addiction [104,172]. However, we extend upon these hypotheses and posit that chronic drug exposure enhances phasic dopamine release, attenuates basal tonic dopamine levels, and promotes aberrant stimulus-reinforcer associations that are important in the development of addiction. Our model fits within the framework of most contemporary theories of dopamine function. Specifically, the increase in the ‘signal to noise’ of phasic dopamine signaling could be interpreted as an enhanced motivation to pursue drugs [35], or may reflect a potentiation in the incentive-value of drug-related stimuli [33], or could provide a ‘prediction-error’ teaching signal that reinforces certain behaviors [36]. However, we believe that the suggested augmented phasic dopamine release after drug experience is likely not involved in learning per se [34,38], as the stimulus-reinforcer associations have already been made. While changes in the dopamine system are associated with learning [76,78,79], it can be difficult to ascribe a causal relationship between dopamine and learning [33]. Regardless, our model proposes that an enhanced ‘signal to noise’ in phasic dopamine release after chronic drug experience will promote drug seeking and aberrant behaviors related to cue-stimuli associations. Future studies will be needed to test the predictions in our model. However, recent improvements in FSCV recording strategies now permit voltammetric recordings over months, which will be an

invaluable experimental technique to specifically examine the role of phasic dopamine release in the development of addiction-related behaviors.

Learning Objectives

- The basic anatomy of the VTA dopamine system and common methods to detect dopamine neurons and dopamine release.
- The evidence supporting contemporary theories of dopamine function.
- The role of phasic dopamine release in appetitive behaviors.
- The acute and prolonged effect of abused drugs on dopamine neuron properties, dopamine neuron firing and dopamine release.
- The effect of abused drugs on phasic dopamine release.

Future Research Questions

- Do dopamine neuron firing patterns change in awake, behaving rodents after abstinence from chronic drug exposure?
- Do the patterns and amplitude of phasic dopamine release change after abstinence from chronic drug exposure?
- Is non-drug related learning affected in a phasic dopamine-dependent manner after chronic drug exposure?
- Are there changes in the pattern of phasic dopamine release during the transition from casual to compulsive drug use?

Acknowledgments

This work was completed while under the support of National Institute of Health funds: T32-AA009455 (MJW), F32-DA024540 (JJC), R21-DA021793 (PEMP), and R01-MH079292 (PEMP).

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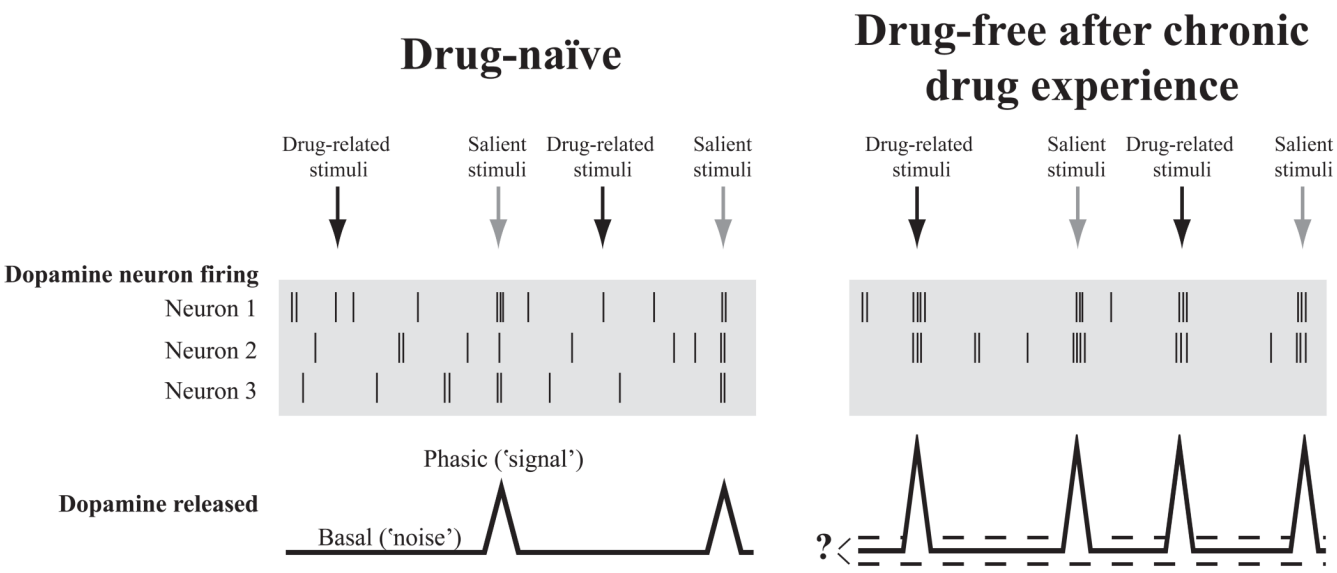

Figure 1.

Schematic representation of changes to the dopamine system after chronic drug experience. (Left) Illustration of the firing patterns of three hypothetical dopamine neurons from a drug-naïve individual where each vertical line represents an action potential. For clarity, there is no distinction between transient increases in firing rate and burst firing, as both are represented by a cluster of action potentials. The specific firing patterns responsible for phasic dopamine release are unknown, but phasic release likely results from coordinated activity of dopamine neurons firing in single-spikes and/or bursts. Notice that behaviorally relevant salient stimuli elicits coordinated activity of dopamine neurons that translates into a phasic increase in dopamine release that could occur in brain regions receiving VTA input, such as the NAcc. However, presentation of drug-related stimuli are without effect on dopamine neuron firing and release in the drug-naïve condition. (Right) After withdrawal from chronic drug treatment, dopamine neuron firing rate and population activity can be reduced, which is represented by fewer spontaneous action potentials and the lack of activity in Neuron 3. While the effect on basal dopamine levels remains controversial, many studies demonstrate instrinsic and synaptic changes on dopamine neurons that could promote the efficacy of glutamatergic inputs on dopamine neurons. We hypothesize that these intrinsic and synaptic changes will increase dopamine neuron firing and phasic release in response to drug-related stimuli. We propose that this increased 'signal to noise' of phasic dopamine release to basal dopamine levels contributes to the aberrent processing of drug-related stimuli, which in turn can promote drug seeking.