Dopamine Signaling in the Nucleus Accumbens of Animals Self-Administering Drugs of Abuse

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Contents

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Abstract Abuse of psychoactive substances can lead to drug addiction. In animals, addiction is best modeled by drug self-administration paradigms. It has been proposed that the crucial common denominator for the development of drug addiction is the ability of drugs of abuse to increase extracellular concentrations of dopamine in the nucleus accumbens (NAcc). Studies using *in vivo* microdialysis and chronoamperometry in the behaving animal have demonstrated that drugs of abuse increase tonic dopamine concentrations in the NAcc. However, it is known that dopamine neurons respond to reward-related stimuli on a subsecond timescale. Thus, it is necessary to collect neurochemical information with this level of temporal resolution, as achieved with *in vivo* fast-scan cyclic voltammetry (FSCV), to fully understand the role of phasic dopamine release in normal behavior and drug addiction. We review studies that investigated the effects of drugs of abuse on NAcc dopamine levels in freely moving animals using *in vivo* microdialysis, chronoamperometry, and FSCV. After a brief introduction of dopamine signal transduction and anatomy and a section on current theories on the role of dopamine in natural goal-directed behavior, a discussion of techniques for the *in vivo* assessment of extracellular dopamine in behaving animals is presented. Then, we review studies using these techniques to investigate changes in phasic and tonic dopamine signaling in the NAcc during (1) response-dependent and -independent administration of abused drugs, (2) the presentation of drug-conditioned stimuli and operant behavior in self-administration paradigms, (3) drug withdrawal, and (4) cue-induced reinstatement of drug seeking. These results are then integrated with current ideas on the role of dopamine in addiction with an emphasis on a model illustrating phasic and tonic NAcc dopamine signaling during different stages of drug addiction. This model predicts that phasic dopamine release in response to drug-related stimuli will be enhanced over stimuli associated with natural reinforcers, which may result in aberrant goal-directed behaviors contributing to drug addiction.

Keywords Dopamine · Drug self-administration · Drugs of abuse · Nucleus accumbens · Drug addiction · Fast-scan cyclic voltammetry · Phasic and tonic dopamine signaling

1 The Dopamine System: Implication in Normal Behavior and Addiction

1.1 Drug Addiction and Dopamine Neurotransmission in Humans

Abuse of psychoactive substances can lead to drug addiction, a maladaptive behavioral pattern of drug use that is often accompanied by drug tolerance and withdrawal symptoms and causes impairment, distress, and the habitual intake of the drug regardless of the devastating consequences (Diagnostic and Statistical Manual of Mental Disorders (DSM-IV); APA 2000). An estimated 5% of the world's population aged 15–64 years used illicit psychoactive drugs in the past year (UN 2008). Legal psychoactive drugs, such as alcohol and tobacco, are used by at least one-quarter of the world's adult population (UN 2008). Drug addiction is considered to be a chronic disorder because addicts are rarely able to maintain abstinence for extended periods of time despite an expressed desire to stay drug-free. This is because stress, re-exposure to the drug itself, and drug-associated cues often trigger the resumption of drug taking (Kalivas and McFarland 2003). Such cues can even promote drug-seeking behavior outside of awareness that eventually results in relapse to drug taking (Tiffany and Carter 1998).

Evidence shows that drugs of abuse affect dopamine neurotransmission. Imaging studies revealed that drug-naïve individuals show enhanced dopamine levels in the striatum upon exposure to psychostimulants such as cocaine and amphetamine (Volkow et al. 1997a; Drevets et al. 2001). In contrast, decreased striatal dopamine responses were reported in detoxified cocaine abusers (Volkow et al. 1997b). Furthermore, individuals with a history of abuse of alcohol (Volkow et al. 1996), cocaine (Volkow et al. 1990), heroin (Wang et al. 1997), or methamphetamine (Volkow et al. 2001) display lower levels of dopamine receptor binding compared to nonabusers (Volkow et al. 2004). Together, these imaging studies suggest an involvement of dopamine neurotransmission in the acute and long-term effects of abused drugs.

1.2 Drug Self-Administration as an Animal Model for Drug Addiction

To better understand the neurobiology of drug abuse and addiction in humans, several animal models have been developed to investigate different aspects of drug addiction (Koob and Le Moal 2008). Among these models, paradigms that incorporate self-administration of drugs are thought to best capture the human condition because animals are allowed to voluntarily seek the drug and because drugs that are self-administered by animals correspond well with those that have high abuse

potential in humans (Koob and Le Moal 2008). However, a great number of studies have examined the effects of drugs of abuse upon passive injection by the experimenter (noncontingent or response-independent administration). Therefore, in this chapter, we will review studies that have used contingent or response-dependent (self-administration), as well as noncontingent or response-independent drug injections.

1.3 Drug-Self-Administration and Dopamine in the Nucleus Accumbens

Dopamine neurotransmission is highly implicated in the regulation of reinforcement in rodent drug self-administration paradigms. The dopamine projection from the ventral tegmental area (VTA) to the nucleus accumbens (NAcc) has been identified as a critical substrate for the expression of drug reinforcement (Ritz et al. 1987; Wise and Bozarth 1987; Koob and Bloom 1988; Kalivas and McFarland, 2003). For example, direct dopamine receptor agonists are self-administered systemically as well as locally into the NAcc (Yokel and Wise 1978; Woolverton et al. 1984; Carlezon et al. 1995). Dopamine receptor antagonists administered systemically in low doses increase the rate of operant responding for cocaine in animals (De Wit and Wise 1977; Ettenberg et al. 1982; Roberts and Vickers 1984; Britton et al. 1991; Corrigall and Coen 1991; Caine and Koob 1994; Hemby et al. 1996), but decrease the motivation to carry out high work requirements to obtain an infusion of cocaine (Hubner and Moreton 1991; Richardson et al. 1993). Similarly, intracerebral administration of dopamine antagonists into the NAcc increases the rate of psychostimulant self-administration (Maldonado et al. 1993; Phillips et al. 1994), but decreases responding when work requirements for the drug infusion increase (McGregor and Roberts 1993). These effects have been interpreted as an attenuation of the reinforcing properties of the drug, such that more drug is taken to achieve the same level of reward, and that less effort is invested into a drug infusion with decreased rewarding properties. In contrast, lesion or inactivation of the mesolimbic dopamine system in the VTA (Roberts and Koob 1982; Shoaib et al. 1998; Xi and Stein 1999) or the NAcc (Roberts et al. 1977, 1980; Lyness et al. 1979; Pettit et al. 1984; Corrigall et al. 1992; Shoaib et al. 1998) attenuate cocaine, amphetamine, heroin, and nicotine self-administration in rats. These findings further underline the critical importance of the mesolimbic dopamine system in drug taking. However, there are some conflicting reports on whether dopamine antagonists or lesions of the mesolimbic dopamine system affect responding for all drugs of abuse (Pettit et al. 1984; Hemby et al. 1996; Di Chiara 2000; Czachowski et al. 2001). Notably, the response of the NAcc dopamine system to drug administration (discussed later) differs significantly depending on whether the animal actively self-administers a drug of abuse or whether the animal receives it independent of a response (Hemby et al. 1995, 1997; Lecca et al. 2007).

1.4 Anatomy of the Dopamine System and Dopamine Signal Transduction: Phasic and Tonic Release

The VTA and the neighboring substantia nigra are the primary dopamine-producing nuclei in the brain (Swanson 1982). From these midbrain nuclei, relatively distinct dopamine cell groups innervate different functional domains of the striatum; i.e., sensorimotor, associative, and limbic circuits that are mainly defined by their differential cortical inputs (Carlsson et al. 1962; Dahlstrom and Fuxe 1964; Alexander and Crutcher 1990; Joel and Weiner 2000). The VTA predominantly projects to the limbic striatum including the NAcc. More than three-quarters of this mesolimbic projection stems from dopaminergic neurons (Swanson 1982).

Dopamine acts on D1- or D2-type dopamine receptors upon release from dopaminergic fibers that densely innervate the striatum (Doucet et al. 1986; Ritz et al. 1987; Groves et al. 1994). Dopamine receptors are found at symmetric boutons formed by dopaminergic terminals on the neck or shaft of the spines of striatal projection neurons (Levey et al. 1993; Groves et al. 1994; Hersch et al. 1995; Caille et al. 1996). However, dopamine receptors are often found on striatal dendrites outside such synapses, in the vicinity of asymmetric boutons on the head of dendritic spines that are contacted by glutamatergic terminals (Levey et al. 1993; Caille et al. 1996). Stimulation of dopamine receptors is terminated by reuptake of extracellular dopamine into the presynaptic terminals. Most dopamine reuptake sites are located on dopaminergic fibers outside synaptic contacts of dopaminergic terminals (Nirenberg et al. 1996; Hersch et al. 1997), similar to the dopamine receptors. Together, this distribution of receptors and reuptake sites allows for "volume transmission"; i.e., the activation of extrasynaptic dopamine receptors by dopamine that diffuses a few micrometers away from its release into the synaptic cleft (Garris et al. 1994; Garris and Rebec 2002; Rice and Cragg 2008). Therefore, the measurement of extracellular dopamine concentrations is a meaningful indicator of dopamine signaling.

Dopamine neurons are either hyperpolarized/quiescent or display different patterns of discharge activity: single-spike firing (2–10 Hz) or bursts of 2–6 action potentials (15–30 Hz) (Grace and Bunney 1984a, b; Freeman and Bunney 1987). Individual dopamine neurons can switch from one of these patterns to the other, as shown in freely moving rats (Freeman and Bunney 1987; Hyland et al. 2002). Salient sensory stimuli can evoke a transient increase in firing rate and burst firing (Freeman and Bunney 1987; Mirenowicz and Schultz 1996). The "tonic" extracellular concentration of dopamine, ranging from 5 to 20 nM depending on the target area, is thought to arise from basal dopamine neuron firing patterns, which predominantly consists of single-spike firing (Bunney et al. 1991; Grace 1991; Parsons and Justice 1992; Keefe et al. 1993; Floresco et al. 2003). Conversely, burst firing of dopamine neuron populations is thought to give rise to "phasic" dopamine events which can reach as high as 1 μM (Gonon 1988; Chergui et al. 1994; Garris et al. 1997). In support of this assertion, it has been shown that electrical stimulations mimicking burst firing are much more potent in triggering dopamine overflow than

single pulse stimulations (Wightman and Zimmerman 1990; Chergui et al. 1996; Gonon and Sundstrom 1996). In summary, the signaling modes that govern communication between dopamine neurons and their target cells are rapid and transient increases in dopamine concentrations (phasic dopamine) on top of a low, slowly changing dopaminergic tone (tonic dopamine).

1.5 Proposed Functions of Dopamine in the NAcc

Since the identification of dopamine over 50 years ago (Carlsson et al. 1957), a number of ideas have been developed to explain the role of dopamine in behavior. These ideas (some of which are presented below) are not necessarily mutually exclusive, but rather focus on different aspects of dopamine function in behavior. The most uncontroversial of ideas is that dopamine is implicated in motor function (Berridge 2007; Salamone and Correa 2002) as selective degeneration of dopamine neurons in Parkinson's disease patients or animals treated with neurotoxins causes motor deficits (Sundstrom et al. 1990; Schwarting and Huston 1996; Galvan and Wichmann 2008). However, these motor deficits are considered to be caused primarily by compromised dopamine signaling in the dorsal striatum, whereas dopamine in the ventral striatum including the NAcc is assumed to be part of a "limbic motor interface" (Mogenson et al. 1980). This idea is based on the fact that NAcc neurons receive input from limbic brain regions and send output to motor brain regions. For example, dopamine infused into the NAcc caused an increase in locomotion that can be inhibited by blocking the effect of NAcc output in one of its motor output nuclei (Jones and Mogenson 1980), supporting the proposition that NAcc dopamine serves as a modulator in the translation of motivation into action (Mogenson et al. 1980).

1.5.1 Dopamine and Motivated Behavior

Mogenson's pioneering work inspired research that produced many lines of evidence supporting a critical role of dopamine in motivation and effort (Salamone and Correa 2002; Berridge 2007). For example, the impact of manipulations that impair dopamine signaling in the NAcc on food-seeking behavior is critically dependent upon the work requirements of the task (e.g., Salamone et al. 1991; Cousins and Salamone 1994). Thus, food-seeking that requires low effort is largely unaffected by partial NAcc dopamine depletions, whereas food-seeking that requires high effort is substantially impaired (e.g., Salamone et al. 1994; Denk et al. 2005). This suggests that dopamine may be implicated in overcoming the motivational costs required for completing tasks that involve a high level of effort (Salamone and Correa 2002; Phillips et al. 2007). Similarly, we recently suggested that NAcc dopamine, influenced by internal deprivation states (e.g., hunger and thirst), plays a key role in overcoming response costs by modulating activity originating from the frontal cortical systems that assess costs and rewards (Phillips et al. 2007). This may

enable mesolimbic dopamine to energize goal seeking and affect cost-benefit decision making.

The "incentive-salience" hypothesis of dopamine also builds upon the involvement of dopamine in motivation (Robinson and Berridge 1993; Berridge 2007). In short, incentive salience is the neural representation of motivational value in response to a reward-related stimulus that drives behavior. Dopamine in the NAcc is thought to modulate the incentive value of such reward-related stimuli (Berridge 2007). The hypothesis distinguishes between "liking" of rewards (hedonic value) and "wanting" of rewards (incentive value) (Berridge 2007). For example, enhancing dopamine levels in dopamine transporter knock-down mice increases the "wanting" of food reinforcers (Pecina et al. 2003; Cagniard et al. 2006a), whereas "liking" of food reinforcers is not affected by insults to the function of the dopamine system (Berridge et al. 1989; Pecina et al. 1997). This supports the proposition that NAcc dopamine is implicated in "wanting" or the "incentive value" of a stimulus.

1.5.2 Dopamine and Reinforcement Learning

The most compelling line of evidence for a role of dopamine in reinforcement learning comes from the firing patterns of dopamine neurons during the presentation of conditioned and unconditioned stimuli (Schultz et al. 1997). Initially, these neurons show synchronous firing patterns in response to the delivery of unpredicted rewards. After repeated pairing with a stimulus that predicts reward, dopamine neurons cease firing to reward delivery and instead respond to the cue that predicts its availability (Schultz et al. 1997; Waelti et al. 2001). This firing pattern of dopamine cells is consistent with a reward prediction signal that provides the organism with the capacity to compare the expected outcome to the actual outcome, in order to maximize reward (Montague et al. 2004). An unexpected reward following a neutral cue is a positive error and favors learning. The omission of an expected reward after a predictive cue or action is a negative error and favors extinction. In support, it has been shown that dopamine neuron firing correlates with the magnitude of the reward (Tobler et al. 2005). However, some have argued it is unlikely that dopamine serves as a teaching signal given the limited availability of afferent sensory processing and the precise timing of dopamine signals (Redgrave and Gurney 2006). Instead, it has been suggested that dopamine may contribute to a more simple, low-computation process, leading to the identification of which aspects of context and behavioral output are crucial in causing unpredicted events (Redgrave and Gurney 2006).

All of the above presented evidence and theoretical framework implicate NAcc dopamine in motivation and/or reinforcement learning. What becomes evident after examining these different lines of research is that the mesolimbic dopamine system is associated with a diverse array of behaviors, which illustrate that dopamine may mediate various functions depending upon the temporal dynamics, location, and context of its release (Schultz 2007). Specifically, the functional impact of phasic and tonic dopamine release may differ, as we will explore below.

2 Dopamine Detection in the Behaving Animal: *In Vivo* Microdialysis, Chronoamperometry, and Fast-Scan Cyclic Voltammetry (FSCV)

A number of analytical techniques are utilized to chemically detect extracellular dopamine *in vivo*. These techniques differ in their time resolution ranging from milliseconds to hours. Thus, some are best suited to detect tonic changes, while others are optimized for isolating phasic dopamine release events.

2.1 In Vivo Microdialysis

Microdialysis is one of the most commonly used methods for the *in vivo* detection of dopamine and has excellent analyte selectivity and sensitivity. In microdialysis, extracellular dialysates of the brain are sampled through a membrane that is permeable to water and small solutes (Bito et al. 1966). The inside of the microdialysis probe inserted into the brain region of interest is continuously flushed with an isomolar solution that lacks the analyte of interest. The analyte of interest is sampled after diffusion from the extracellular space across the membrane into the microdialysis probe and thus changes in concentration can be detected. Another variant of this technique used for determining the absolute basal analyte concentrations is no-net flux microdialysis, which involves perfusion of known concentrations of the analyte of interest through the probe to establish when an equilibrium between the inside and the outside of the probe is reached (Parsons and Justice 1992). Despite the considerable size of the microdialysis probe (0.2–0.5 mm in diameter; 1–2 mm working length), several experimental studies indicate that the damage to the blood–brain barrier is minimal (e.g., Westerink and De Vries 1988; Tossman and Ungerstedt 1986).

Microdialysis is a sampling technique that is not directly coupled to any particular method of chemical analysis. The vast majority of studies uses high performance liquid chromatography in conjunction with electrochemical or fluorescence detection to analyze the very small amount of chemicals in the dialysate. Due to this small amount of dialysate, the sampling time-resolution is usually between 5 and 20 min. Even though there are now technical advances that will enable sample collection in intervals significantly shorter than a minute (Bowser and Kennedy 2001), most microdialysis experiments still operate on relatively low temporal resolution and are best suited for the quantitative analysis of basal and slowly changing tonic dopamine concentrations.

2.2 Electrochemical Techniques

It is known that dopamine neuron activity responds to reward-related stimuli on a subsecond timescale (Schultz et al. 1997). To fully understand control of behavior

by dopamine in the NAcc and its role in drug addiction, we require neurochemical information with this level of temporal resolution. Electrophysiological recordings provide excellent temporal resolution but usually do not determine the projection target of recorded neurons, and thus cannot inform us on neurotransmission in specific terminal structures. In contrast, electrochemical or voltammetric techniques combine sampling of dopamine neurotransmission in specific terminal structures with excellent temporal resolution.

Although various voltammetric methods have been developed over the years, the basic principle underlying each of these variations is the application of a modest electrical potential sufficient to drive electrolysis of the analyte of interest in brain extracellular fluid (Adams 1976; Stamford 1986; Kawagoe et al. 1993). The current produced by this electrolysis can be measured at the electrode and is proportional to the number of molecules undergoing oxidation, and therefore to the concentration of analyte at the electrode surface (Adams 1976; Stamford 1986; Kawagoe et al. 1993). Adams and coworkers pioneered voltammetric recordings of dopamine in the 1970s (Adams 1976). However, the presence of high concentrations of electroactive neurotransmitter metabolites, as well as ascorbic acid and uric acid, interfered with their recordings (Marsden et al. 1988). Technical advances such as the utilization of modified electrodes and more complex input voltage command waveform to improve selectivity (e.g., Gonon et al. 1981; Gonzalez-Mora et al. 1991) have led to the development of three predominant techniques for high-temporal resolution monitoring of dopamine using carbon-fiber microelectrodes: (a) amperometry, (b) high-speed chronoamperometry, and (c) FSCV (Garris and Rebec 2002). These techniques are now often referred to as voltammetric techniques. They are very attractive tools for chemical monitoring in the brain because measurements can be made with a small probe (5–30 μm in diameter; less than 200 μm working length) that causes minimal tissue damage and allows for sampling in precise brain areas. Considering the size of the carbon fiber electrode and the size of the synaptic cleft (15–25 nm; Savtchenko and Rusakov 2007), it is evident that voltammetry monitors the dopamine overflow in the extrasynaptic extracellular space and not dopamine in the synaptic cleft. Of these techniques, (constant-potential) amperometry is the fastest and "simplest" as it applies a continuous, constant potential to the electrode. Although this variant has microsecond temporal resolution, it offers little chemical selectivity since current produced by oxidation of any compound will be detected. Thus, amperometry is of great utility in studying, for example, fast release and uptake kinetics of single cells in brain slices (e.g., Chow et al. 1992), but has found little use in behaving animals. The remaining two techniques are reviewed below.

2.2.1 *In Vivo* Chronoamperometry

In chronoamperometric recordings, the potential of the working electrode is stepped up, held at this higher potential, and then stepped back down, while the resulting oxidation and reduction currents from faradic processes occurring at the

electrode are monitored. Such currents have either been analyzed on the level of seconds (for simplicity here termed: high time resolution) or averaged to achieve a better signal-to-noise ratio with a time resolution of minutes to hours (low time resolution). Because electroactive species have different chemical reversibilities, a ratio of oxidation and reduction currents (redox ratios) can assist in identifying the primary substance contributing to changes in the electrochemical signal (e.g., Gratton et al. 1989). Chemical sensitivity is improved further in this technique by using electrodes coated with Nafion, an ion-selective polymer, (Gerhardt et al. 1984) that reduces the contribution of anionic species such as ascorbic acid and the dopamine metabolite dihydroxyphenylacetic acid (DOPAC) to the signal.

2.2.2 *In Vivo* FSCV

Compared to chronoamperometry, FSCV is a more selective electrochemical method, because it utilizes a triangle input waveform (and not a step function) to separate electrolysis from different analytes into temporally resolved peaks in the output current. Since the voltage is swept gradually to an oxidizing potential and back, current is generated over time, during oxidation and reduction processes, whereby producing multiple electrochemical peaks for an ideal compound. This allows for the recording of a chemical signature, the voltammogram, that serves to identify the species detected, separating the signal from changes in pH and "other noise" and making the chemical resolution more robust (e.g., Baur et al. 1988, Michael et al. 1998). The voltammogram has sufficient information that it can be used with high-powered statistical analysis and provides standardized identification of the dopamine signal (Heien et al. 2004). For this chemometric approach, a so-called "training set" of phasic dopamine events of different amplitude spanning the concentration range of interest is collected (stimulated electrically with varying pulse rate and frequency). This training set is then used to perform a principal component analysis of the signal to statistically identify dopamine events.

3 Effects of Drugs of Abuse on Extracellular Dopamine Concentration in the NAcc

3.1 The Dopamine Hypothesis of Addiction

It has been proposed that the critical mechanism for the development of addiction is drug-induced activation of dopamine transmission in the NAcc, also referred to as the "dopamine hypothesis of addiction" (Fibiger et al. 1987; Wise and Bozarth 1987; Di Chiara and Imperato 1988). Electrophysiological studies have shown that acute exposure to many drugs of abuse affect the firing properties of dopamine neurons in the VTA despite their many distinct actions in the brain (for review, see Wanat et al. in press). However, to directly study dopamine signaling in the NAcc

and to fully characterize the functions of dopamine in this target region, it is essential to study dopamine release into the extracellular space (discussed later) in addition to dopamine cell firing.

3.2 Drug Effects on Dopamine Signaling Measured Over the Course of Minutes: Microdialysis Studies

In the following sections, we will focus on studies investigating the effects of abused drugs on dopamine levels in the NAcc in freely moving animals. Microdialysis studies in behaving animals demonstrated that response-independent, systemic administration of cocaine, amphetamine, heroin, cannabinoids, nicotine, and ethanol increase dopamine levels in the NAcc (Di Chiara and Imperato 1986; Imperato and Di Chiara 1986; Imperato et al. 1986; Di Chiara and Imperato 1988; Kalivas and Duffy 1990; Kuczesnki et al. 1991; Yoshimoto et al. 1992; Pontieri et al. 1996; Tanda et al. 1997). The dose of the drug administered and the concentration of striatal dopamine following drug administration are positively correlated, as demonstrated for cocaine and ethanol (Nicolaysen et al. 1988; Bradberry 2002). Similar to response-independent drug administration, self-administered drugs of abuse, including cocaine, amphetamine, heroin and ethanol, induce increases in concentrations of dopamine in the NAcc (Hurd et al. 1989, 1990; Pettit and Justice 1989, 1991; Weiss et al. 1992, 1993; Di Ciano et al. 1995; Wise et al. 1995a, b). Conversely, drugs with low potential for abuse do not affect dopamine overflow (Di Chiara and Imperato 1988). These findings are in agreement with the dopamine hypothesis of addiction (see Sect. 3.1), since drugs of abuse increase tonic concentrations of extracellular dopamine in the NAcc.

During psychostimulant self-administration, animals learn to "load up" drug concentrations with an initial burst of operant responses before settling into a slower, more regular pattern of responding with inter-response rates varying between 2 and 20 min (Carelli and Deadwyler 1996). Response rates are inversely related to the infusion dose of cocaine or amphetamine; thus, the lower the dose the higher the number of responses (Pickens and Thompson 1968; Wilson et al. 1971; Yokel and Pickens 1973; Wise and Bozarth 1987; Di Ciano et al. 1995). However, the total intake of these drugs is elevated with higher doses. This intake pattern seems not to be due to aversive drug effects at high doses, since monkeys will choose infrequent high doses in preference to more frequent low doses (Iglauer et al. 1976) and rats show no reliable preference for one over the other (Di Ciano et al. 1995). Furthermore, animals will adjust their response rates to meet increased operant response demands (Roberts et al. 1989). Together, this suggests that animals titrate their drug intake to achieve a preferred level of intoxication.

Cocaine-induced increases in extracellular NAcc dopamine concentrations are thought to be the principal neurochemical event associated with the drug's positive reinforcing action (see Sect. 1.3; Kuhar et al. 1991; Wise and Bozarth 1987; Roberts et al. 1977; Ritz et al. 1987). For example, psychostimulants are self-administered

directly into the NAcc (Hoebel et al. 1983; MCkinzie et al. 1999), and morphine and ethanol into the VTA (e.g., Bozarth and Wise 1981; Gatto et al. 1994). With increased drug dose the dopamine "maintenance" concentration in the NAcc is also held at an increased level (Pettit and Justice 1991). Importantly, microdialysis studies have shown that animals will maintain the increased NAcc dopamine concentration during cocaine, amphetamine, and heroin self-administration sessions at a steady level over days, just like they maintain the drug concentrations at a steady level (Pettit and Justice 1989; Pettit et al. 1990; Wise et al. 1995a, b; Ranaldi et al. 1999). Furthermore, in a microdialysis study with advanced temporal resolution that sampled dopamine every minute, Wise et al. (1995b) demonstrated that the self-administration pattern of cocaine closely followed NAcc dopamine levels within sessions. This study demonstrated that cocaine dose-dependently increased dopamine concentrations after an infusion and that rats self-administered the next infusion as soon as the dopamine concentration diminished past a certain threshold. Consistent with this finding, it has been proposed that functional dopamine depletion in the NAcc represents a neurochemical correlate of drug craving (Dackis and Gold 1985; Koob et al. 1989). The findings presented above suggest that fluctuation in tonic dopamine concentration in the NAcc is a common denominator between different abused drugs that can regulate drug self-administration behavior.

3.3 Drug Effects on Dopamine Signaling Measured Over the Course of Seconds to Hours: Chronoamperometry Studies

In vivo chronoamperometry studies in the behaving animal have demonstrated that experimenter-administered ethanol, cocaine, and amphetamine increase extracellular concentrations of dopamine over the course of minutes to hours (Kiyatkin 1994; Di Ciano et al. 1998b; Sabeti et al. 2003). Similarly, self-administration of heroin and psychostimulants caused an increase in dopamine concentrations in the NAcc on this time scale (Gratton 1996; Di Ciano et al. 2001, 2002). Thus, chronoamperometry studies with low time resolution confirmed microdialysis findings on the basic effects of abused drugs on extracellular concentration of dopamine in the NAcc.

To further investigate the temporal dynamics of dopamine signaling in animals self-administering drug, chronoamperometry with high time resolution was used to monitor dopamine on the order of seconds. NAcc dopamine concentrations were found to gradually increase preceding and to drop immediately following response-dependent (and -independent) intravenous injections of cocaine, before rising again around 4–6 min after infusion (Kiyatkin and Stein 1994, 1995). These postresponse decreases in signal were dose-dependent, absent when the infusion was withheld, and the preresponse increases became increasingly bigger when the access to the lever was blocked (Kiyatkin and Stein, 1993; Kiyatkin and Gratton 1994; Gratton 1996). Furthermore, chronoamperometry studies reported similar response patterns during operant behavior maintained by other reinforcers such as heroin

(Kiyatkin and Stein 1993) and food (Kiyatkin and Gratton 1994), supporting the assumption that dopamine is the principal contributor to the reported biphasic signal fluctuations. In summary, the described high time resolution chronoamperometric data are in conflict with microdialysis findings which found that dopamine levels in the NAcc rise and fall in unison with oscillating blood/brain stimulant levels (Pettit and Justice 1989; Koob and Bloom 1988; Wise and Bozarth 1987; see Sect. 3.2).

The validity of chronoamperometry measurements has been challenged on the basis of chemical sensitivity (Salamone 1996; Di Chiara 2002; Wightman and Robinson 2002). First, even though the electrodes are much less sensitive to DOPAC than to dopamine, the DOPAC concentration is several hundred times higher than dopamine and fluctuations in DOPAC concentration may contribute to the signal (Dayton et al. 1981; Gonon et al. 1984). Second, the voltage input step used to measure current changes that were assumed to be due to the oxidation/reduction of dopamine also measures changes in pH that often accompany dopamine signaling (Heien et al. 2004). The argument that chemical species other than dopamine are contributing to the chronoamperometry signal is supported by the fact that the detected task-related signaling changed dramatically during the development of self-administration behavior (Gratton 1996), an observation not reported for heroin or by microdialysis studies with cocaine. Furthermore, chronoamperometry studies report drug-induced elevations in dopamine concentrations last nearly twice as long as that measured with microdialysis (Di Ciano et al. 1995). Although these results were replicated and the reported electrochemical changes were shown to be task-related, one cannot be sure about the chemical specificity of the signal (Wightman and Robinson 2002), especially in light of evidence from a microdialysis study reporting the opposite finding (Wise et al. 1995b; see Sect. 3.2).

In summary, microdialysis and low time resolution chronoamperometry studies have convincingly demonstrated a link between tonic dopamine concentrations in the NAcc and the reinforcing effects of drugs of abuse. However, both techniques also raised questions. For example, what is the detailed temporal composition of dopamine signals? In contrast, chronoamperometry with high temporal resolution leaves the question of the chemical identity of observed phasic changes unanswered. These questions and some of the above described issues are not resolvable with these techniques, as the need for a combination of high temporal and chemical resolution is not satisfied by either of these techniques alone.

3.4 Drug Effects on Dopamine Signaling Measured on a Subsecond Time Scale: FSCV Studies

3.4.1 Changes in Phasic Dopamine Signaling to Response-Independent Drug Administration

FSCV provides sufficient temporal and chemical resolution to study phasic dopamine signals. For example, a single phasic dopamine event in response to either

electrical stimulation or presentation of a salient stimulus can be assessed. Furthermore, FSCV can examine the effects of drugs of abuse on phasic dopamine in both in vitro (slice) and in vivo (anesthetized, awake, and during self-administration) preparations, and can separate dopamine release and uptake. In addition to the amplitude and duration of phasic dopamine changes, the frequency of "spontaneous" dopamine transients (i.e., phasic release events found in the awake animal that are not attributed to specific events in the animal's environment) can also be measured. Thus, findings obtained with FSCV illustrate a greater complexity of dopamine signaling than previously described by data from other techniques (see Sects. 3.2 and 3.3).

The phasic NAcc dopamine response to ethanol and cannabinoids illustrates the complexity in the profile of subsecond dopamine signaling. Ethanol showed no effect on dopamine uptake in striatal brain slices collected from drug-naïve rats (Samson et al. 1997; Budygin et al. 2001b; Mathews et al. 2006), but enhanced dopamine uptake in animals chronically treated with ethanol, possibly due to a compensatory mechanism resulting from elevated dopamine levels (Budygin et al. 2007). Consistent with this, both ethanol and cannabinoids attenuate electrically stimulated dopamine release in the intact animal, possibly due to increased tonic dopamine levels (see Sect. 3.2) that impair phasic dopamine release due to activation of release-regulating autoreceptors (Budygin et al. 2001a; Cheer et al. 2004). In contrast, intravenous infusions of ethanol and cannabinoids increased the amplitude and/or frequency of spontaneous phasic dopamine transients in awake, behaving animals (Cheer et al. 2004, 2007). These findings suggest that the complexity conferred by multiple mechanisms make it difficult to parsimoniously use findings from in vitro preparations and artificial electrical stimulations to make net predictions concerning the effect of drugs on phasic dopamine signaling in awake, behaving rodents. In agreement with results presented in Sect. 3.2 that indicated enhanced tonic dopamine concentrations in the NAcc, the findings presented above demonstrate increased frequency of spontaneous phasic dopamine signals by ethanol and cannabinoids.

A number of FSCV 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 of the anesthetized rat (Middleton et al. 2004). Nicotine exerts frequency-dependent effects on electrically stimulated phasic dopamine release in vitro; at low firing rates dopamine release is attenuated, but at high firing rates nicotine enhances dopamine release (Zhang and Sulzer 2004). Intravenous infusions of nicotine also increase the frequency and amplitude of spontaneous phasic dopamine release events in the behaving rat (Cheer et al. 2007). Together, both in vitro and in vivo studies consistently show enhanced phasic dopamine signaling in response to nicotine.

Consistent with findings from other abused substances, intravenous infusions of cocaine increase amplitude and frequency of spontaneous phasic dopamine release events in the NAcc (Heien et al. 2005; Stuber et al. 2005a, b; Cheer et al. 2007; Wightman et al. 2007; Aragona et al. 2008), as well as the amplitude of electrically

stimulated release (Wu et al. 2001). An increase in amplitude can be explained by decreased reuptake due to the pharmacological action of cocaine. However, it is not clear why cocaine increases the frequency of dopamine release events. It seems likely that more phasic signals exceed the FSCV detection threshold due to their increased amplitude and thus become "visible" under drug exposure. Another explanation is that drug-induced behavioral hyperactivity may stimulate afferents to the VTA, and therefore may increase the firing frequency of dopamine neurons projecting to the NAcc. Notably, these findings indicate that the strong increases in tonic dopamine levels described in Sect. 3.2 do not appear to result in significant autoreceptor-mediated inhibition of dopamine neurons; thus, one could describe the phasic signals as "riding on a tonic dopamine wave" during drug exposure.

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 (Cheer et al. 2007). While the locus of this effect is yet to be determined, it is speculated that cannabinoid receptor activation in the VTA reduces GABA release on dopamine neurons (Riegel and Lupica 2004). These findings suggest that abused drugs exert similar effects on phasic dopamine release even though their respective pharmacological and cellular effects are quite distinct.

3.4.2 Changes in Phasic Dopamine Signaling During Cocaine Self-Administration: The Role of Operant Behavior and Conditioned Stimuli

Pavlovian and operant conditioning paradigms using nondrug reinforcers have demonstrated that conditioned stimuli (CS) can elicit phasic dopamine release (Roitman et al. 2004; Day et al. 2007; Stuber et al. 2008; Owesson-White et al. 2008). In studies using drug reinforcers, it has been shown that repeated CS presentation with drug delivery subsequently can elicit an electrochemical response when the CS is presented alone (Kiyatkin and Stein, 1993; Kiyatkin and Gratton 1994; Di Ciano et al. 1998a). This response develops over time, as its development requires at least 10–50 pairings of the drug with the CS (Gratton 1996), and therefore indicates that these dopamine signals reflect a learning process. Studies that probed the contribution of CS to phasic dopamine in response to drug taking will be discussed below.

Contingent and noncontingent cocaine administration produce differential long-term effects on synaptic plasticity in VTA dopamine neurons (Chen et al. 2008). The effect of cocaine infusions on phasic dopamine release also depends on whether the drug administration is contingent upon an operant response or not, as shown with FSCV (Stuber et al. 2005a). For example, in rats pressing a lever for an intravenous infusion of cocaine, rapid changes in dopamine concentrations are time-locked to specific aspects of this behavior (Phillips et al. 2003; Stuber et al. 2005a, b; Fig. 1a), whereas no changes in dopamine levels are observed within 10 s of a response-independent cocaine administration to awake, but idle rats (Stuber et al. 2005a).

In contrast, following these initial 10 s, the frequency of spontaneous dopamine transients increases dramatically independent of whether the administration of the drug was response-independent or -dependent (Stuber et al. 2005a). However, there is an ongoing debate regarding the exact latency of the pharmacological effects of cocaine after intravenous infusion (Espana et al. 2008; Wise et al. 2008). The considerable variance in the onset of these transients may be due to variability in the latency of drug delivery to the brain. Together, this suggests that (a) early dopamine release events (first 10 s) in animals that self-administered cocaine may be related to learned associations and (b) the increase in spontaneous dopamine transients 10 s after the beginning of the infusion may be a consequence of the pharmacological effects of cocaine that are not related to learning. Consistent with this idea, these latter spontaneous transients are correlated with cocaine levels and the animal's locomotion (Stuber et al. 2005a). In summary, cocaine self-administration is accompanied by early phasic dopamine release that is time-locked to the onset of drug infusion but cannot be attributed to the pharmacological effects of the drug.

Phillips et al. (2003) demonstrated that the largest change in dopamine concentration time-locked to cocaine self-administration behavior occurs immediately upon completion of the operant response (Fig. 1a). This effect was conditioned to an audiovisual stimulus (presented on the completion of the lever response) and was not due to the pharmacological actions of cocaine since it persisted during initial extinction trials where cocaine is replaced with saline (Stuber et al. 2005b; Fig. 1b). If the CS denoting the onset of the cocaine infusion was presented noncontingently during the period between operant responses, a similar dopamine signal could be evoked. Furthermore, this signal diminished gradually when the associative strength between the stimuli and cocaine is weakened during extinction (Stuber et al. 2005b; Fig. 1b). This phenomenon is identical to what has been observed with nondrug reinforcers, where cues that predict availability of these reinforcers are able to elicit phasic dopamine release on their own (Roitman et al. 2004, Owesson-White et al. 2008). Therefore, the change in extracellular dopamine that occurs at completion of the operant response (Fig. 1a) may encode the association of cue and drug delivery, and thus the expectation of cocaine delivery.

Phasic dopamine release has also been demonstrated just prior to the operant response for a self-administered infusion of cocaine (Phillips et al. 2003, Stuber et al. 2005a, b; Fig. 1a). These changes tended to be smaller than those following the operant response, but consistently preceded the animal's approach to the response lever. In agreement with these antecedent neurochemical signals, dopamine neuron activation also occurs immediately before subsequent injections in rats trained to bar press for intravenous heroin (Kiyatkin and Rebec 2001). Furthermore, chronoamperometric studies detected a slow increase in dopamine-related signals (over the course of multiple seconds) in rats before they approached the lever for the next drug self-administration (Kiyatkin and Stein 1995). This temporal correlation with the drug seeking (lever approach) suggests that this component of the neurochemical signal might be causally linked to the behavior (Phillips et al. 2003, Stuber et al. 2005a, b). The temporal proximity of the signal precludes testing its role in drug seeking using conventional pharmacological approaches, since blockade of

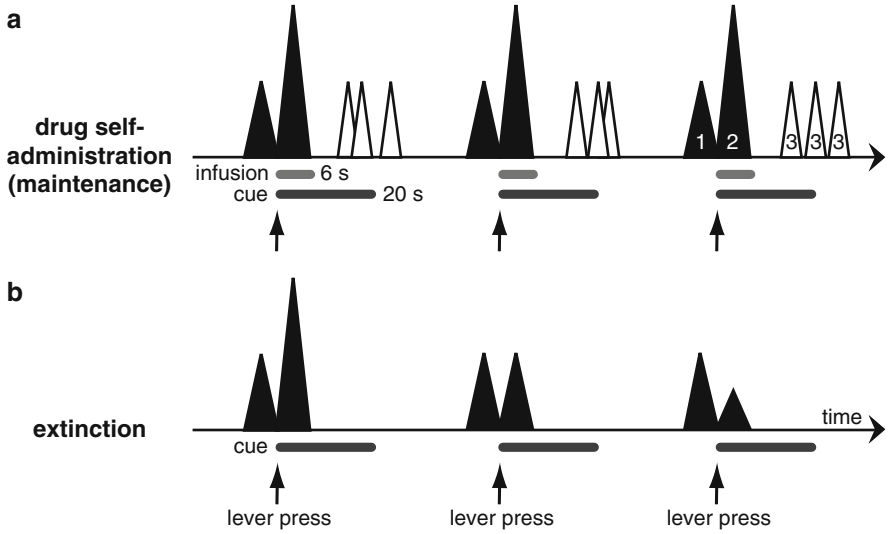

Fig. 1 Phasic dopamine signaling in the NAcc associated with drug seeking and taking. (**a**) Phasic dopamine signaling consists of multiple phasic events (triangles). The first event is elicited by the animal's approach of the operant lever (preresponse signal) (1), whereas a bigger second event is associated with the onset of the audiovisual cue (dark gray bar) that is presented in response to the lever press (postresponse signal) (2). A set of peaks (3) that is observed with an onset of approximately 10 s after the lever press and the beginning of the drug infusion (light gray bar), is thought to be a direct consequence of the pharmacological effect of the drug. The latency of this pharmacological effect relative to the operant response appears to be more variable than for the postresponse signal. (**b**) During extinction, the audiovisual stimulus presented after the lever press is not accompanied by a drug infusion. As a consequence, the postresponse dopamine signal becomes smaller with repeated nonreinforced responding. In contrast, the preresponse signal remains relatively stable during extinction. This suggests that the preresponse signal reflects the motivation to obtain drug, whereas the postresponse encodes the expectation of the drug infusion

this signal will perturb other phasic dopamine signals or the tonic baseline level of dopamine. However, an electrically evoked dopamine signal of similar brevity was sufficient to promote the lever approach (drug seeking), as such brief changes in dopamine, heavily influenced drug seeking by biasing the animal to initiate this behavior (Phillips et al. 2003). This may indicate a role for phasic dopamine in drug seeking or at least biasing the animal's decision-making policies towards selecting actions leading to drug taking, rather than a direct role in drug reward. In contrast to the postresponse signal, this preresponse signal does not appear to be a learned or conditioned process because it does not disappear during extinction trials, where the CS was presented contingent to the operant response but without drug infusion (Stuber et al. 2005b; Fig. 1b). Together, these findings indicate that the preresponse dopamine signal may be involved in initiating approach behavior.

In summary, these findings underline the multiple roles of phasic dopamine in operant responding for cocaine. Phasic dopamine release associated with operant behavior is comprised of signals in relation to approach, conditioned cues, and the

pharmacological effects of the drug (Fig. 1a). Dopamine signaling is likely to play a role in motivation, but probably also encodes other information about goal-directed behavior including learned association between cues and drug reward. The extinction-resistant preresponse signal seems to be related to drug seeking, and therefore may have a motivational quality. In contrast, the postresponse signal is linked to a learned association (lever-press and cue signaling the drug infusion), and therefore may be related to the expectation of drug delivery (see Sect. 3.4.2). Compared to natural reinforcers, such behavior-related dopamine release is enhanced due to the pharmacological properties of abused drugs. Therefore, the normal function of these signals is potentially corrupted, which may explain dysregulated goal-directed behavior in addiction (see Sect. 7.2).

3.5 Summary

The findings obtained in FSCV studies examining the effects of different drugs of abuse on phasic dopamine signaling in the NAcc are in general agreement with findings made with microdialysis and low time resolution chronoamperometry (see Sects. 3.2 and 3.3), as each of these techniques have shown that response-dependent and -independent administration of abused drugs increase dopamine levels in the NAcc. Thus, both phasic and tonic concentrations of dopamine in the NAcc are enhanced by drugs, which is in agreement with the postulate of the dopamine hypothesis of addiction that drugs of abuse converge on the mesolimbic dopamine pathway. These findings also raise the question as to what extent such phasic events contribute to the observed changes in tonic dopamine levels. Some evidence indicates that spontaneous dopamine transients that presumably reflect the pharmacological effects of drugs are likely to alter overall tonic dopamine concentrations (see Sect. 3.4.2). Future studies are required to investigate a possible interaction between phasic and tonic dopamine signaling and to examine phasic dopamine release during the self-administration of a wider range of abused substances.

4 Effects of Withdrawal from Drugs of Abuse on the NAcc Dopamine System

While the acute effects of drugs on the dopamine system are well cataloged, the long-term effects after cessation of drug intake are less well studied and understood. This disconnection in the research is partly because the latter effects show considerable variance that arises from the drug studied, how the drug is administered (dose, frequency, and route), and duration of abstinence after drug experience (Wanat et al. in press). It has been documented that repeated exposure to a drug of abuse causes structural changes in VTA dopamine neurons, as repeated opiate

exposure decreases the size and caliber of dendrites and soma of VTA dopamine neurons (Sklair-Tavron et al. 1996). Along with such structural changes, many studies support the notion that multiple drug exposures lead to an altered function of the dopamine system (Koob and Le Moal 2008), though the timing of this effect can vary.

4.1 Tonic Dopamine During Withdrawal

Microdialysis studies have demonstrated that the discontinuation of chronic treatment with ethanol (Rossetti et al. 1991, 1992a, b; Diana et al. 1993; Weiss et al. 1996), morphine (Acquas et al. 1991; Pothos et al. 1991; Acquas and Di Chiara 1992; Rossetti et al. 1992a, b; Crippens and Robinson 1994), nicotine (Rahman et al. 2004), amphetamine (Rossetti et al. 1992a), or cocaine (Parsons et al. 1991; Robertson et al. 1991; Imperato et al. 1992; Rossetti et al. 1992a, b; Segal and Kuczenski 1992; Weiss et al. 1992; Diana et al. 1993; Chefer and Shippenberg 2002; Zhang et al. 2003) decreases the basal extracellular concentration of dopamine in the NAcc.

However, there have been conflicting reports for withdrawal from psychostimulants. For example, several studies demonstrated a lack of change in basal concentrations of NAcc dopamine after withdrawal from amphetamine (Segal and Kuczenski 1992; Crippens et al. 1993; Crippens and Robinson 1994; Paulson and Robinson 1996). In the case of cocaine, some studies reported that withdrawal does not change tonic NAcc dopamine (Robinson et al. 1988; Kalivas and Duffy 1993; Hooks et al. 1994; Meil et al. 1995; Kuczenski et al. 1997), and yet others found an increase in basal dopamine levels (Imperato et al. 1992; Weiss et al. 1992; Johnson and Glick 1993; Heidbreder et al. 1996). While some studies reported changes in basal dopamine levels depending upon the time of cocaine withdrawal (Imperato et al. 1992; Heidbreder et al. 1996), these observed changes have not been consistent across studies. For example, some report that withdrawal after chronic cocaine exposure decreases basal dopamine levels in as early as a few hours (Zhang et al. 2003) to as long as 10 days (Parsons et al. 1991), while others found increases in basal dopamine levels during 1–4 days of withdrawal (Imperato et al. 1992; Weiss et al. 1992; Heidbreder et al. 1996), and it was reported to have no effect on basal dopamine levels after 24 h and 2 weeks withdrawal (Kalivas and Duffy 1993; Meil et al. 1995). Thus, at least for cocaine, no clear temporal effect of withdrawal on basal dopamine levels can be inferred from these studies. The studies described above utilized either conventional microdialysis or the more accurate method of determining exact basal dopamine levels, no-net flux microdialysis (Parsons and Justice 1992). The majority of studies employing no-net flux microdialysis did not observe changes in dopamine levels after withdrawal from cocaine treatment, strongly supporting no or minor effects of cocaine withdrawal on tonic dopamine concentration (Crippens et al. 1993; Kalivas and Duffy 1993; Heidbreder et al. 1996; Chefer and Shippenberg 2002).

Together, the effects of withdrawal from chronic drug treatment on NAcc dopamine levels depend on many factors, including the drug studied and the dose of the drug administered during the chronic treatment (Kalivas and Duffy 1993). In addition, it is known that tonic dopamine levels in the NAcc are affected by drug cues (see Sect. 5.1) and by contextual cues associated with aversive stimuli (Mark et al. 1991; Saulskaya and Marsden 1995). Re-exposure to a drug-paired environment can either be rewarding or aversive depending on drug dose and time of drug-cue pairing after drug administration (Ettenberg 2004). Differences in these parameters may explain some of the discrepancies between studies presented here. In summary, according to microdialysis studies the NAcc dopamine system may undergo a depression after withdrawal from abused substances; however, this finding remains controversial regarding psychostimulants such as cocaine.

4.2 Phasic Dopamine During (Short-Term) Withdrawal

Only one study using FSCV has examined how phasic dopamine release associated with drug taking is affected by withdrawal from drug self-administration. Stuber et al. (2005b) showed that the dopamine postresponse signal associated with the completion of the operant response gradually decreases during an extinction session immediately after completion of a cocaine self-administration session, whereas the preresponse signal remained relatively stable (Fig. 1b). Thus, the overall phasic dopamine release associated with the operant response for drug delivery decreases during withdrawal. However, this study does not reveal how phasic dopamine signals are affected by long-term withdrawal. Furthermore, the self-administration behavior underwent extinction instead of abstinence, a better model for the human condition because humans do not usually undergo extinction during drug withdrawal. The term "abstinence" will be used here to describe withdrawal from drug taking without extinction of drug taking behavior. We are aware of the fact that this term is not an ideal description of animal behavior since the animal does not refrain from drug taking voluntarily. Future studies should investigate changes in phasic dopamine signaling during long-term withdrawal after extinction or abstinence from drug taking.

Collectively, these studies suggest that acute exposure to drugs of abuse activates phasic and tonic dopamine signaling in the NAcc (see Sect. 3), but withdrawal from chronic drug exposure can dampen phasic and tonic dopamine levels in the absence of drug (see Sect. 4). However, withdrawal from psychostimulants does not necessarily lead to decreased tonic levels. Decreased tonic levels of dopamine in the NAcc and firing of VTA dopamine neurons during drug withdrawal have been shown to return to and above basal levels by a subsequent drug re-exposure with ethanol (Diana et al. 1993; Weiss et al. 1996), amphetamine (Robinson et al. 1988), cocaine (Pettit et al. 1990), and morphine (Sklair-Tavron et al. 1996; Diana et al. 1999). Similarly, the extinction-induced decrease of the phasic postresponse dopamine signal can be reversed to previous amplitudes during a drug-induced

reinstatement session, as shown by FSCV (Stuber et al. 2005b). Returning dampened dopamine levels to "baseline" may be one of the driving forces in relapse to drug taking behavior, since evidence presented in Sect. 3.2 indicates that animals pursue the next drug infusion when tonic dopamine levels in the NAcc decrease past a certain threshold.

5 Stimulus-Induced NAcc Dopamine Release in the Absence of Drug: Implications for Reinstatement of Drug Seeking

5.1 Effects of Drug Cues on Tonic Dopamine Concentration in the NAcc

In the previous sections, we reviewed the powerful effects of abused drugs on dopamine signaling in the NAcc during drug taking and withdrawal. This leads to the question of whether the NAcc dopamine system is also involved in reinstatement of drug seeking behavior after abstinence or extinction of drug taking. Re-exposure to drugs of abuse on a single occasion can promote relapse to drug seeking behavior in abstinent human drug users (Jaffe et al. 1989). Similarly, exposure to a CS associated with self-administered drugs can elicit subjective states such as craving (Grant et al. 1996; Childress et al. 1999; Garavan et al. 2000), as well as drug seeking and relapse in humans (Stewart et al. 1984; Avants et al. 1995) and experimental animals (Markou et al. 1993, Robinson and Berridge 1993). Furthermore, even after extinction of self-administration behavior, drug seeking can be reinstated in animals by presentation of conditioned drug cues (e.g., de Wit and Stewart 1981; Weiss et al. 2000).

It has been proposed that the ability of conditioned drug cues to increase dopamine is critical for reinstatement of drug seeking (Stewart et al. 1984), and support for this assumption is provided by findings in animals (see Sect. 3.4.2). Further evidence for the involvement of NAcc dopamine signaling in drug-induced reinstatement is provided by findings demonstrating that microinjection of amphetamine into the NAcc can reinstate heroin self-administration (Stewart and Vezina 1988) and that such drug seeking can be attenuated by drugs that decrease dopamine neuron activity (Di Ciano and Everitt 2003, 2004; Bossert et al. 2004). In contrast, a decrease in the concentration of extracellular dopamine in the NAcc may contribute to some drug withdrawal symptoms (Rossetti et al. 1992b). Decreasing withdrawal symptoms by increasing dopamine levels may therefore possibly promote the motivation to reinstate drug taking (Koob and Le Moal 2008). Therefore, we will now focus on studies examining drug cue-induced changes in dopamine release and how this relates to reinstatement of drug seeking.

Several studies have observed increases in tonic dopamine concentrations in the NAcc following the noncontingent presentation of a psychostimulant-paired CS in the absence of drug. Such CS-induced effects were demonstrated after pairing of

the CS with response-independent (Fontana et al. 1993; Di Ciano et al. 1998b) as well as with response-dependent (Gratton and Wise 1994; Kiyatkin and Stein 1996; Di Ciano et al. 1998a; Ito et al. 2000) drug administration. Similar conditioned changes in dopamine have been shown in the NAcc following the noncontingent presentation of stimuli previously paired with food (Young et al. 1998), heroin (Gratton 1996), or footshock (Wilkinson et al. 1998). In contrast to noncontingent presentation, response-contingent presentation of a CS failed to produce changes in tonic NAcc dopamine (Neisewander et al. 1996; Ito et al. 2000). In fact, one study found no difference in NAcc dopamine concentrations during cocaine self-administration without concurrent presentation of the CS as compared to self-administration of cocaine plus contingent presentation of a CS (Bradberry et al. 2000). However, it should be noted that other studies have found no change in tonic dopamine efflux in response to the noncontingent presentation of drug cues (Brown and Fibiger 1992; Bradberry et al. 2000). This discrepancy may be due to the proximity of changes in dopamine concentrations to the microdialysis detection limit, where minor differences in the study design, for example, the number of stimulus-reward pairings or CS presentations, may cause different outcomes. Overall, these findings suggest that noncontingent (but not contingent) presentation of drug-paired cues can contribute to overall changes in tonic NAcc dopamine.

Few studies have examined dopamine release during actual cue-induced reinstatement of drug-seeking after abstinence or extinction of the operant behavior. One study found elevations in tonic NAcc dopamine after extinction in conjunction with robust cocaine-seeking behavior elicited by sustained (60 min) presentation of a salient discriminate stimulus that previously signaled the availability of cocaine (Weiss et al. 2000). In contrast, reinstatement elicited by brief noncontingent presentation of a visual drug cue during or after extinction did not produce significant changes in dopamine efflux, although drug-induced reinstatement showed both a behavioral and a neurochemical response (Neisewander et al. 1996; Di Ciano et al. 2001). This suggests that repeated or sustained noncontingent presentation of drug-associated cues may be necessary to elicit changes in tonic dopamine concentrations during reinstatement of drug seeking that are detectable with microdialysis.

5.2 *Effects of Drug Cues on Phasic Dopamine Signaling in the NAcc*

There are no studies to date that have examined cue-induced reinstatement of drug seeking with FSCV. However, Stuber et al. (2005b) demonstrated that the phasic dopamine component that occurs following a lever-press for cocaine infusion (postresponse) gradually diminishes during extinction, whereas the signal that occurs just prior to the lever-press (preresponse) seems resistant to extinction (Fig. 1b, see Sect. 4.2). During drug-induced reinstatement, postresponse but phasic dopamine release returns to the previous pre-extinction amplitude, suggesting that

it encodes a learned association between cue and drug delivery (Stuber et al. 2005b). In addition, studies recording neuronal firing in the NAcc during within-session extinction have shown that neurons with a postresponse discharge pattern are less active during extinction and return their activity to pre-extinction levels after reinstatement (Carelli and Ijames 2000). The absence of the postresponse signal after extinction in both striatal dopamine release and NAcc cell firing makes it an unlikely candidate as the driving force behind the initiation of the reinstatement of drug seeking. Moreover, the increase in postresponse dopamine does not cause further cocaine seeking in self-administration maintenance sessions, as it would be expected if this aspect of the dopamine signal is involved in approach behavior or drug seeking. Instead the animals typically engage in stereotypies during the immediate postresponse phase before seeking the next infusion (Stuber et al. 2005a). However, abstinent human addicts generally do not undergo extinction, and thus drug cues may retain their capacity to elicit dopamine release. Furthermore, the postresponse signal may reappear during subsequent extinction sessions, as drug seeking in response to drug cues is not permanently extinguished after a single extinction session, as shown in many studies (Shalev et al. 2002).

In contrast to the postresponse dopamine signal, the preresponse dopamine signal may be an essential component of reinstatement of drug seeking since it remains relatively stable during extinction (Fig. 1b), and an electrically evoked dopamine signal of similar brevity is sufficient to induce drug seeking (Phillips et al. 2003). Additionally, animals will approach and press a lever for an infusion of dopamine into the NAcc (Dworkin et al. 1986). Such a dopamine-induced approach response may be more reliably triggered in a drug-related environment where the approach is directed towards a familiar goal.

Together, the findings presented in Sects. 5.1 and 5.2 indicate that tonic and phasic dopamine concentrations in the NAcc can be increased during (noncontingent) cue-induced reinstatement of drug seeking. However, there have been few studies of this effect and their findings are somewhat inconsistent, which may reflect the highly dynamic quality of the phasic dopamine postresponse that fades quickly under extinction conditions. The lack of reinstatement-related tonic dopamine changes after brief exposure to drug cues under extinction conditions may thus be attributable to a diminished amount of phasic dopamine per lever approach (decreased postresponse dopamine), whereas higher tonic dopamine levels can be achieved with sustained cue exposure. These findings suggest that the more stable preresponse component of the dopamine signal (Fig. 1b) may be of greater significance in eliciting reinstatement of drug seeking.

6 The Role of NAcc Dopamine in Drug Addiction

Altered dopamine signaling has been implicated in all stages of drug addiction, from induction to maintenance to relapse. Unlike natural reinforcers, drugs act directly on the mesolimbic dopamine system thereby bypassing sensory processing and

adaptive mechanisms that normally control NAcc dopamine release. Most theories of drug addiction postulate that this "direct access" to dopamine signaling results in abnormal shaping of synaptic efficiency. However, addiction theories differ regarding the effect that these processes have on the organism (discussed later).

6.1 Motivation and Addiction

The "incentive-sensitization" theory of addiction proposed by Robinson and Berridge (1993) emphasizes the motivational function of NAcc dopamine. It states that hedonic processes ("liking") associated with drug intake are not mediated by the mesolimbic dopamine projection, which instead is involved in the attribution of incentive salience to stimuli associated with rewards ("wanting") (as described in Sect. 1.5.1). Thus, this theory postulates that NAcc dopamine mediates the motivation to pursue rewards. Addictive drugs are assumed to render these brain reward systems hypersensitive (i.e., "sensitized") to drugs and drug-related stimuli, causing pathological wanting of drugs. According to this view, relapse to drug seeking and compulsive aspects of drug taking are mediated by the sensitized dopamine efflux in the NAcc in response to a drug-paired CS.

6.2 Associative Learning and Addiction

Dopamine receptors regulate intracellular signaling cascades that alter the expression of genes, such as immediate-early genes, which are considered to be one of the first molecular steps that ultimately result in stable neuroadaptations and behavioral changes (for review, see Davis and Squire 1984; Stork and Welzl 1999; Tischmeyer and Grimm 1999). In the striatum, such mechanisms have been shown to play a central role in learning-related changes in protein synthesis (Teather et al. 2005; Hernandez et al. 2006). Consistent with associative learning theories of addiction, psychostimulants engage a set of molecular mechanisms normally implicated in learning and memory including D1 receptors and downstream intracellular messenger cascades that may cause synaptic rearrangements (Berke and Hyman 2000; Everitt et al. 2001). Thus, psychostimulant-induced dopamine release may alter learning-related molecular changes by activating common signal transduction pathways. In fact, the effects of psychostimulants on procedural memory consolidation have been demonstrated in many studies (e.g., Puglisi-Allegra et al. 1994; Castellano et al. 1996; Cestari and Castellano 1996; Packard and White 1991). Importantly, recent studies found D1 receptor-dependent effects of cocaine on procedural learning in association with molecular changes in the striatum (Willuhn and Steiner 2006, 2008). A current influential hypothesis that incorporates these findings would suggest that addiction is due to drug-induced neuroadaptations in reward-related learning and memory processes in the NAcc (Berke and Hyman 2000; Everitt et al. 2001). Such neuroadaptations are believed to cause

hypersensitivity to cocaine-associated cues (Di Chiara and Bassareo 2007; Everitt and Wolf 2002) and abnormal habit-like behaviors (White 1996) that become insensitive to adverse consequences with chronic drug exposure and lead to compulsive drug intake (Wolffgramm and Heyne 1995; Deroche-Gamonet et al. 2004).

7 Different Functions for Phasic and Tonic Dopamine Transmission in Addiction

How can the different modes of dopamine transmission, phasic and tonic signaling, be synthesized with different theories of addiction? Most experiments do not distinguish between these two modes of neurotransmission. For example, in vivo microdialysis and low time resolution chronoamperometry measure changes in tonic levels of dopamine, but it is not clear how much phasic signaling contributes to tonic extracellular concentrations of dopamine, and, thus, these techniques potentially measure the sum of both tonic and phasic dopamine. Similarly, pharmacological manipulations of the dopamine system modify both tonic and phasic aspects of dopamine neurotransmission, as both modes presumably utilize the same mechanisms of release and reuptake. Interestingly, it is both experimentally and conceptually challenging to separate the different functions of dopamine on a behavioral level. As described in Sect. 1.5, dopamine signaling is thought to be implicated in both reinforcement learning and motivation. Dopamine is thought to facilitate reinforcement learning by "stamping in" stimulus-reward associations (Wise 2004), providing a prediction error (Montague et al. 2004), and/or by biasing action selection (Redgrave and Gurney 2006). Alternatively, dopamine is thought to facilitate motivation by enhancing the energizing effect of reward or reward-predicting cues through assignment of incentive salience (Robinson and Berridge 1993, 2008) and/or by maintaining behavior when response costs are high (Salamone and Correa 2002). Later, we argue that the different temporal modes of dopamine signaling fulfill both learning and motivational functions.

Recent research, using a genetic approach, indicates that phasic and tonic dopamine signaling may indeed subserve different functions. Specifically, reduced expression of the dopamine transporter in the striatum and thus reduced clearance of released dopamine has been shown to cause increased motivation in a previously learned task in the absence of new learning (Cagniard et al. 2006b). Importantly, mice carrying this inducible knockdown of the dopamine transporter showed increased nonbursting activity of dopamine neurons (presumably driving tonic dopamine concentration in the striatum) but no change in burst firing (presumably driving phasic dopamine release). Thus, these mice learned a behavioral task and were then rendered tonically hyperdopaminergic, which led to a better performance in this task without affecting reinforcement learning subsequently tested in another task (Cagniard et al. 2006b). This important finding suggests that tonic dopamine signaling may mediate motivational aspects of behavior. Conversely, it has been suggested that phasic signaling is particularly well suited for transmitting rapid

time-specific information and thus provide the temporal resolution necessary to represent the contingencies in reinforcement learning (Grace 1991; Schultz 2007). FSCV recordings in the NAcc were made from rats during Pavlovian reinforcement learning support this role for phasic dopamine release (Day et al. 2007; Sunsay and Rebec 2008; Stuber et al. 2008). Early in training, phasic dopamine responses are observed primarily with reward delivery (unconditioned stimulus, US). With continued training, dopamine release is elicited by the presentation of the CS, while the response to the US is attenuated, suggesting a transfer of the phasic dopamine response from the US to the CS (Day et al. 2007; Sunsay and Rebec 2008). Such a role for dopamine in the learning of stimulus–reward associations has also been demonstrated in electrophysiological studies (Schultz et al. 1997; see Sect. 1.5.2) and cocaine self-administration studies using FSCV, as discussed in Sect. 3.4.2 (Phillips et al. 2003; Stuber et al. 2005a, b). However, phasic dopamine is also associated with initiating goal-directed behaviors, and thus may have a motivational impact as well (see Sect. 3.4.2; Phillips et al. 2003). Therefore, phasic signaling, time-locked to drug intake and drug-predicting stimuli, may contribute to both the motivational aspects of drug taking and associative learning related to drug taking. Together, these findings suggest that different time scales of dopamine transmission may have different functions, where different aspects of phasic signaling is related to both reinforcement learning and approach behavior (motivation), and tonic signaling enables motivational and motor systems but not reinforcement learning.

7.1 Dopamine Signaling in the Drug-Naïve State (Fig. 2a)

In Fig. 2, we summarize data reviewed in this chapter in a simplified manner and discuss it in light of the theoretical framework of NAcc dopamine function reviewed in Sects. 1.5 and 6. In a drug-naïve state (Fig. 2a), it is assumed that NAcc neurons receive physiological levels of receptor stimulation by tonic dopamine release providing normal motivational function of the organism. Phasic dopamine release and subsequent postsynaptic dopamine receptor stimulation may alter synaptic plasticity on striatal projection neurons (in concert with glutamate signals) in response to behaviorally relevant novel stimuli and natural reinforcers. Together this allows for normal goal-directed behavior and reinforcement learning. In this drug-naïve state (Fig. 2a), stimuli that are specifically associated with drug intake, such as drug paraphernalia or cues predicting drug availability, will not affect dopamine neuron firing or release because the organism has not yet been exposed to the drug.

7.2 Immediate Effects of Drug Exposure (Fig. 2b)

Thus far, we have reviewed data demonstrating that acute exposure to drugs of abuse increases phasic (see Sect. 3.4) and tonic dopamine concentrations (see

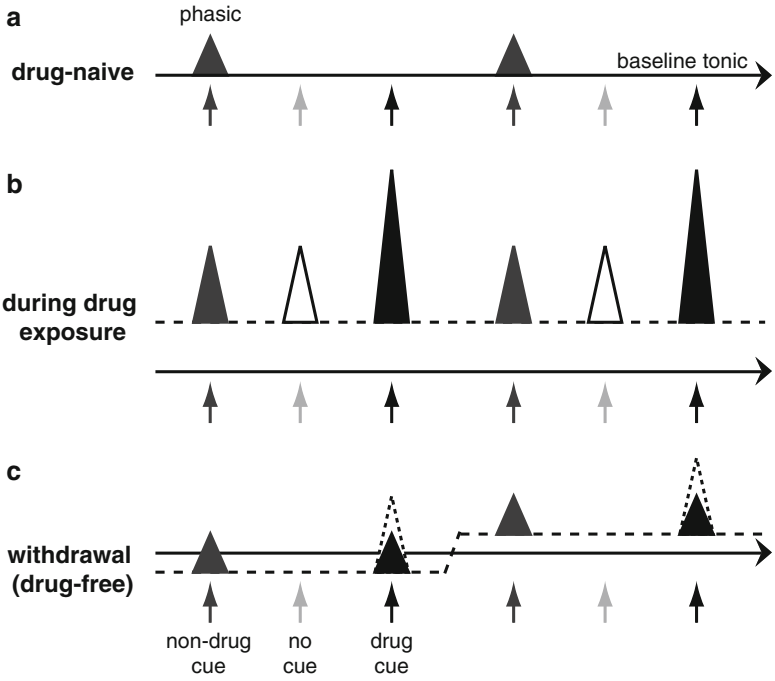

Fig. 2 Drug-induced changes in phasic and tonic dopamine transmission in the NAcc. (**a**) In the drug-naïve state, phasic (triangles) and tonic (solid horizontal line) dopamine signaling in the NAcc is normal. Few spontaneous phasic dopamine events (no cue) are observed. Salient stimuli (nondrug cues) can elicit phasic dopamine release and goal-directed behavior. (**b**) Drugs of abuse enhance tonic (dashed line) and phasic (triangles) dopamine signaling. Stimuli not associated with drug (nondrug cues) and drug-related cues both elicit phasic dopamine events, but the latter cause more robust release due to the temporal proximity to the drug administration. Furthermore, the number of spontaneous phasic dopamine events is increased. This may lead to aberrant learning of drug-cue associations and thus abnormal goal-directed behavior such as compulsive drug taking. (**c**) Effects of drug withdrawal on dopamine signaling are variable. For example, dampened tonic dopamine concentrations during withdrawal can be returned to and above basal concentrations by exposure to drug cues and drug context (left to right). Such drug cues may also elicit more phasic dopamine release (dashed triangle) compared to nondrug cues because (1) drugs represent a higher reward magnitude than natural reinforcers and/or (2) extended withdrawal results in incubation of drug craving. As a consequence, independent of tonic dopamine levels, seeking for drugs is more prevalent than seeking for natural reinforcers, which may promote relapse to drug taking

Sect. 3.2 and 3.3) in the NAcc. What are the potential behavioral consequences of this enhanced dopamine signaling? During drug exposure, cues predicting reinforcer availability may elicit greater amounts of dopamine due to the drug-induced increase in the amplitude of phasic dopamine signals, similar to cocaine-induced increases in electrically stimulated release (Wu et al. 2001; Figs. 2a, b). Notably, exposure to cocaine and amphetamine also affects the processing of cues that are not related to drug intake (e.g., Puglisi-Allegra et al. 1994; Castellano et al. 1996; Cestari and Castellano 1996; Packard and White 1991). Additionally, the number of

spontaneous phasic dopamine release events is increased dramatically due to the pharmacological effect of the drug which possibly leads to an association of an increased number of environmental stimuli with the drug experience (see Sect. 3.4). Together, this may explain how contextual cues not directly predicting drug administration become powerfully associated with the drug experience. In comparison to natural reinforcers and contextual cues, drug-associated cues are even more robustly "consolidated" due to the high contiguity and contingency of drug administration and these cues (i.e., the drug-induced facilitation of dopamine signaling is strongest immediately after intake and drug cues are never experienced separately from drug administration) (Fig. 2b). Consistent with this idea, learning associations between cues and natural reinforcers transiently affects the synaptic properties of dopamine neurons, while drug experience promotes long-lasting changes to the intrinsic and synaptic properties of dopamine neurons (Chen et al. 2008; Stuber et al. 2008). Such facilitation in Pavlovian learning may then promote the development of abnormal levels of dopamine release by drug-conditioned stimuli upon re-exposure (Redish 2004; Di Chiara and Bassareo 2007).

With repeated training on a Pavlovian learning task using a natural reinforcer, the phasic dopamine signal shifts from reward delivery to the cue that predicts it (Day et al. 2007; Schultz et al. 1997). In contrast, dopamine signals in response to drug delivery in a drug self-administration task may not attenuate or may attenuate slower than with natural reinforcement because drugs directly activate the dopamine system. Therefore, this teaching signal may be constantly exhibited to both drug cues and the drug delivery itself. Thus, the brain continues to perceive drug delivery as a novel reward or positive prediction error despite repeated use (Redish 2004). Additionally, drug reward may be experienced as a reward of exaggerated magnitude, and thus the positive prediction error may be extraordinarily large (Tobler et al. 2005). Together, this may lead to aberrant reinforcement learning and eventual fixation on pursuit of drugs and compulsive intake.

If dopamine acts to promote the repetition of actions that immediately precede rewarding events (Redgrave and Gurney 2006), drug exposure would immensely facilitate operant behavior that leads to drug administration. Alternatively, such drug-enhanced phasic dopamine signaling could also lead to the sensitized attribution of incentive salience to drug-related cues (Robinson and Berridge 1993). Thus, enhanced phasic signaling may promote abnormal responding to drug cues, whether due to aberrant learning and memory or motivation. Enhanced tonic dopamine concentrations may produce more exploratory activity and thus greater exposure of the organism to the drug environment including drug-related cues possibly promoting continued drug intake. This role for tonic dopamine fits well with the proposition that dopamine may have a function in overcoming the motivational costs required for completing tasks (Salamone and Correa 2002; Phillips et al. 2007). Tonically elevated dopamine concentrations may therefore keep the motivational cost for pursuing drug rewards minimal.

Together, we posit that the drug-induced enhancement of phasic dopamine signaling will increase phasic release in response to previously weak or neutral

stimuli and specifically strengthen associations of drug cues and drug delivery, whereas increased tonic dopamine levels may maintain the organisms motivation to continue drug intake by promoting seeking of cues/environments associated with the drug (Fig. 2b).

7.3 *Long-Term Effects of Drug Exposure During Drug Withdrawal (Fig. 2c)*

Withdrawal after chronic drug exposure has variable effects on tonic NAcc dopamine levels (see Sect. 4.1). Some studies report decreased dopamine concentrations while others have found no change or even increased basal levels. Lowered tonic dopamine levels during drug withdrawal may be associated with a reduced motivational state, leading to an enhanced susceptibility to drug seeking elicited by drug cues. Drug seeking could result in further exposure to drug cues, and thus eventually lead to elevated tonic levels of dopamine, as noncontingent presentation of drug-associated cues are known to cause elevations in tonic dopamine levels (see Sect. 5.1; Fig 2c). Increases in tonic dopamine could then, in turn, facilitate seeking behavior.

Although little is known about the effect of drug withdrawal on the frequency or size of phasic dopamine release, we assume based on the findings discussed above that phasic signals to drug cues will be greater compared to (nondrug) cues associated with natural reinforcers (Fig. 2c), due to the abnormally strong association between drug and drug-predicting cues that develops during drug exposure (see Sect. 7.2; Fig. 2b). One explanation for enhanced phasic dopamine release to drug cues is that drugs of abuse produce an exaggerated reward magnitude, which is known to be reflected in dopamine signaling (Tobler et al. 2005). Another possibility is that the dopamine signal to drug cues escalates over time due to incubation of drug craving during abstinence (Grimm et al. 2001). In support of this proposition, it has been demonstrated that the activation of NAcc neurons by drug-associated cues is potentiated after 1 month of abstinence from cocaine self-administration (Hollander and Carelli 2007). Because phasic dopamine release is associated with the initiation of goal-directed behaviors (Roitman et al. 2004; Phillips et al. 2003; Stuber et al. 2005a, b; see Sects. 3.4.2 and 4.2), it follows that promotion of drug seeking in response to drug-related stimuli is more likely than seeking of natural rewards in response to associated nondrug cues. This assumption is consistent with the DSM-IV criterion that human drug addiction normally constitutes a progressive "narrowing" of the behavioral repertoire to that controlled by drug reinforcement rather than that guided by natural reinforcers, such as food or sex. Taken together, we propose that independent of tonic NAcc dopamine concentrations during withdrawal exposure to drug-associated stimuli activates phasic dopamine release more than nondrug related stimuli, and thus leads to fixation on drug-related behavior and eventually relapse to drug taking.

8 Summary

In this chapter, we review the current state of knowledge on how abused drugs, drug-associated cues, drug seeking, and drug withdrawal affect phasic and tonic dopamine signaling in the NAcc in animal models of addiction. For the sake of simplicity, we have neglected to address the core and shell subdivisions of the NAcc (e.g., Zahm and Heimer 1990) and referred to the NAcc as a whole. The vast majority of the reviewed studies sampled dopamine concentrations in the NAcc core. However, greater increases in phasic and tonic dopamine concentrations in the NAcc shell compared to the core have been identified in response to psychostimulants, morphine and ethanol (e.g., Pontieri et al. 1995; Ito et al. 2000; Lecca et al. 2007; Aragona et al. 2008; Howard et al. 2008). Furthermore, it has been shown that dopamine in the shell increases following self-administration of cocaine, but not following presentation of CS associated with the drug, whereas such CS predicting cocaine caused dopamine release in the core (Ito et al. 2000). These data suggest that the NAcc shell may be mainly implicated in the primary reinforcing effects of psychostimulants, whereas the core is preferentially involved in conditioned drug responses.

The reviewed results are integrated with current ideas on the role of dopamine in addiction with an emphasis on a model illustrating phasic and tonic NAcc dopamine signaling during different stages of drug addiction. Each theory of dopamine function briefly outlined in this chapter has merits and it is not our intention to verify or falsify any of them, but rather to combine their different perspectives. The purpose of this chapter is not to provide a new psychology of addiction, but rather to give an updated perspective on potential neurochemical mechanisms underlying addiction. We have only focused on dopamine signaling here, although many other neurochemical systems have been identified as important contributors to addiction. Our model predicts that phasic dopamine release in response to drug-related stimuli will be enhanced over stimuli associated with natural reinforcers, which may result in aberrant goal-directed behaviors contributing to drug addiction.

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