Environmental Modulation of Drug Taking: Nonhuman Primate Models of Cocaine Abuse and PET Neuroimaging

Michael A. Nader[1] and **Matthew L. Banks**[2]

[1]Department of Physiology and Pharmacology, Wake Forest University School of Medicine, Winston-Salem, NC 27157-1083 USA

[2]Department of Pharmacology and Toxicology, Virginia Commonwealth University, Richmond, VA 23298-0613

Abstract

The current review highlights the importance of environmental variables on cocaine self-administration in nonhuman primate models of drug abuse. In addition to describing the behavioral consequences, potential mechanisms of action are discussed, based on imaging results using the non-invasive and translational technique of positron emission tomography (PET). In this review, the role of three environmental variables – both positive and negative - are described: alternative non-drug reinforcers; social rank (as an independent variable) and punishment of cocaine self-administration. These environmental stimuli can profoundly influence brain function and drug self-administration. We focus on environmental manipulations involving non-drug alternatives (e.g., food reinforcement) using choice paradigms. Manipulations such as response cost and social variables (e.g., social rank, social stress) also influence the behavioral effects of drugs. Importantly, these manipulations are amenable to brain imaging studies. Taken together, these studies emphasize the profound impact environmental variables can have on drug taking, which should provide important information related to individual-subject variability in treatment responsiveness, and the imaging work may highlight pharmacological targets for medications related to treating drug abuse.

Keywords

animal models; dopamine; social variables; alternative reinforcers; punishment; PET imaging; nonhuman primates

1. Introduction

Drug abuse continues to be a major public health problem worldwide (WHO, 2004). Recent estimates report between ~4–6% of those surveyed (ages of 15–64 yrs old) used some illicit substance in 2008 (UNODC, 2010). In the United States approximately 22 million people reported drug use, of which ~1.6 million were cocaine users (SAMHSA, 2010). In Europe,

the number of reported cocaine users doubled in the last decade (UNODC, 2010). Despite significant advances in our understanding of the behavioral neuropharmacology of drugs of abuse, successful and sustained treatment strategies, especially for stimulants like cocaine, have not been discovered.

While there are many variables mediating drug taking, in the simplest terms, these could be organized within three general categories: agent, host and environment (O'Brien, 2011). For this review, the primary "agent" we will consider is cocaine, although, it is our belief that the principles described would apply to behavior maintained by other abused drugs, such as methamphetamine and nicotine. The "host" refers to the individual. It is a hallmark of addiction that there are individual differences in response to drugs; a particular advantage of animal models is that these behavioral phenotypes can be systematically and explicitly studied. Finally, "environmental variables" can include alternative reinforcers, social context and punishment; these also can be systematically studied in animal models. While social rank could be considered a host (i.e., organismal) variable, we will consider it as a result of the social environment and treat it as another environmental manipulation. The goal of this review is to highlight the powerful role the environment has on cocaine self-administration in preclinical models, primarily those involving nonhuman primates. Several environmental variables will be examined, including alternative reinforcers, social factors, and punishment. We will also describe in vivo imaging studies that help elucidate the mechanisms of action for these various environmental variables. The aim of this review is to address whether different environmental manipulations that increase or decrease cocaine-maintained behaviors in preclinical models produce similar changes in the brain as measured using in vivo imaging techniques.

1.A. Models of cocaine self-administration

There are several excellent reviews of the use of conditioned and unconditioned behaviors to assess cocaine reinforcement in animals (e.g., Griffiths et al., 1980; Woolverton and Nader, 1990; Koob et al., 1998; Ator and Griffiths, 2003; Banks and Negus, 2012), so this section and subsequent sections will not be exhaustive. Rather, we will focus on the animal models that will be highlighted in this review, which involve cocaine self-administration procedures. Animals will self-administer many of the same drugs that humans abuse and by the same routes, with strikingly similar patterns of intake (Deneau et al., 1969; Griffiths et al., 1980; Ahmed and Koob, 1998, 2005). If responding leading to the presentation of the drug occurs at higher rates than vehicle-maintained responding, the drug is said to function as a positive reinforcer and may have abuse potential. When studying reinforcing effects – i.e., determining whether the drug injection maintains higher rates of responding than vehicle-contingent responding – the most frequently used simple schedule of reinforcement is the fixed-ratio (FR) schedule. Under FR contingencies, the consequent stimulus is delivered following a specified number of responses. Under these conditions, responding is characterized as an inverted U-shaped function of dose (see Pickens and Thompson, 1968; Skjoldager et al., 1991; Zernig et al., 2004).

Measures of reinforcing effects using simple schedules of reinforcement do not allow for direct comparisons between reinforcing stimuli (Woolverton and Nader, 1990). For this purpose, models of reinforcing strength, such as progressive-ratio or concurrent-access choice schedules of reinforcement are frequently implemented. For this review, we will focus on choice paradigms and, in most studies the choice was between cocaine and a non-drug alternative, food (see Banks and Negus, 2012 for a recent review). One of the rationales for food-drug choice studies is the goal of reallocating choice from cocaine to a non-cocaine alternative (Banks et al., 2013). From a translational approach, this model has perhaps the strongest predictive validity to the human condition.

Since Dews (1955) classic study, behavioral pharmacologists have been aware of the powerful role the environment plays in drug effects, including drug self-administration. In this review, we highlight methods that have been shown to increase or decrease drug self-administration in nonhuman primate models: alternative reinforcers, social factors and punishment. We describe the strengths and weaknesses of each approach and we delve into the potential neuropharmacological mechanisms for each, using non-invasive brain imaging protocols (described in the next section). The goal is to highlight how different environmental events that alter cocaine self-administration do so via similar or different neuropharmacological mechanisms.

1.B. Brain imaging protocols in nonhuman primate models

There are several excellent recent reviews involving nonhuman primate imaging studies (Howell and Murnane, 2011; Murnane and Howell, 2011; Gould et al., 2012, 2013). Most of the imaging studies described in this review utilized positron emission tomography (PET), although we do mention other imaging modalities, including those based on magnetic resonance imaging (MRI) (see Nader and Czoty, 2008 for additional imaging rationale for studies involving nonhuman primates). PET imaging involves positively charged subatomic particles (i.e., "positrons") that travel in space (for this review, the space is the brain) in a random fashion until they collide with electrons and are annihilated. The result is gamma particles that project at 180° with an energy of 511keV (i.e., "emission"). PET cameras have detectors that recognize stimulation at 180° and provide information about the location of annihilation in 3D (i.e., "tomography"). The most frequently used radioactive tracers for receptor-based PET studies are ^{11}C (half-life of 20 min) and ^{18}F (half-life of 110 min). Glucose utilization is assessed using ^{18}F fluorodeoxyglucose ($[^{18}$F]FDG). Data are analyzed for a specific region of interest, although whole brain analyses of metabolism and blood flow can also be analyzed, and the distribution volume (DV) is compared to a reference region. The ratio of DV values is the primary dependent variable (referred to as the distribution volume ratio, DVR). It is a unit-less number that reflects receptor availability. Another common dependent variable is the binding potential and this number too reflects both affinity (*Kd*) and the receptor number (*Bmax*).

Many studies use the same PET camera and receptor-based radiotracer in animals and humans, making PET imaging a highly translational research technique. However, one major difference is that the majority of preclinical imaging studies anesthetize the animal prior to and throughout the PET study, while humans are typically studied awake. Although some investigators have conducted awake imaging in monkeys (e.g., Howell et al., 2001, 2002; Murnane and Howell, 2010), depending on the research question, it is not always necessary to use conscious, behaving monkeys in PET imaging studies (see Nader and Czoty, 2008 for additional information). For example, if an investigator is interested in correlating receptor availability, as a trait measure or after some manipulation (a state measure), with some behavioral outcome, using anesthetized subjects can address those research questions. The preclinical studies described in this review only used anesthetized subjects.

2. Alternative reinforcers and cocaine self-administration

While preclinical laboratory studies investigating drugs as reinforcers typically utilize simple schedules of reinforcement, drug vs. non-drug choice procedures have become the standard in clinical studies of drug reinforcement (Haney and Spealman, 2008; Banks and Negus, 2012). Furthermore, interest in drug reinforcement is derived from its presumed role in drug addiction, and drug addiction can be defined as a disorder of choice and behavioral allocation (Heyman, 2009; Hernstein and Prelec, 1992). Moreover, in the fifth edition of the Diagnostic and Statistical Manual of Mental Disorders, six of the 11 diagnostic criteria for

substance dependence are defined as inappropriate behavioral allocation towards the procurement and use of the illicit substance. Thus, drug addiction implies excessive drug choice at the expense of more adaptive behaviors and increased preclinical use of choice procedures might facilitate translational research in the development of effective treatment strategies.

2.A. Behavioral effects of environmental variables using cocaine-food choice paradigms

There are several outstanding reviews on the use of choice paradigms in drug addiction research (e.g., Bergman and Paronis, 2006; Banks and Negus, 2012). We will focus on a few studies that are relevant to imaging studies described in the next section. In one of the first intravenous drug vs. non-drug choice procedure, rhesus monkeys were given a choice between cocaine injections (0.3 mg/kg per injection) and food (five 1.0-g banana-flavored pellets) under conditions in which no other source of food was available outside of the choice procedure (Aigner and Balster, 1978). Over the 8 experimental days, monkeys almost exclusively chose cocaine over food despite body weight losses of 6 to 10%. Specifically, the use of choice procedures in nonhuman primates allowed for the assessment of this excessive behavioral allocation between cocaine and food. An important facet of these findings is that under unlimited access conditions, cocaine preference remained high despite significant decreases in body weight and self-administration of near toxic cocaine doses; the health and physical appearance of the monkeys prompted the investigators to terminate the study. However, under limited access conditions, this dose of cocaine (0.3 mg/kg per injection) vs. 4 food pellets lead to approximately 50% choice in 2 of the 4 monkeys tested (Nader and Woolverton, 1991). Taken together, these two choice studies highlight the significance of environmental variables, such as cocaine availability (limited vs. unlimited), on drug-taking behaviors. Later, we will describe imaging studies in which access conditions of cocaine are the primary independent variable.

Several studies have investigated pharmacological manipulations to decrease cocaine-food choice (e.g., Woolverton and Balster, 1979; Czoty et al., 2005b). For example, Woolverton and Balster (1981) trained rhesus monkeys under a discrete-trials choice procedure to choose between intravenous cocaine and food reinforcement. Continuous infusions of low to intermediate doses of the dopamine (DA) D2-like receptor antagonists chlorpromazine and haloperidol increased choice for the low cocaine doses without affecting high-dose cocaine preference. Higher doses of the D2-like receptor antagonists decreased responding for both reinforcers. As described below, imaging studies have implicated DA D2-like receptors in cocaine abuse, so results from choice studies showing D2-like receptor antagonism is not sufficient to reallocate responding suggests that preclinical pharmacology in the absence of environmental context does not predict clinical efficacy.

More recent studies have demonstrated the importance of other environmental manipulations, such as the magnitude of the alternative nondrug reinforcer, programmed schedule consequences, and delay of reinforcement that could influence drug choice (Elsmore et al., 1980; Nader and Woolverton, 1991; 1992a, 1992b; Negus, 2003; Woolverton and Anderson, 2006; Woolverton et al., 2007, 2012; Banks et al, 2013). For example, increasing the magnitude (i.e., number of pellets) or decreasing the cost (i.e., response requirement) of the alternative food reinforcer has consistently decreased cocaine choice (Nader and Woolverton, 1991, 1992a; Negus, 2003; Banks et al., 2013). These environmental manipulations have important implications for medications development. A recent study highlights this point. Banks et al. (2013) trained rhesus monkeys to choose between various doses of cocaine and food; complete cocaine dose-response curves were determined each session. Next, the effects of chronic treatment with the monoamine releaser phenmetrazine were examined. Cocaine choice was affected only at the highest phenmetrazine dose and was accompanied by decreases in overall operant behavior that may

be interpreted as a potential medication side effect. That is, the decrease in cocaine choice was accomplished by a reallocation of responding to the non-drug alternative, but only at a phenmetrazine dose that also decreased total choice trials completed. Next, manipulations of food and cocaine FR values were made. Increasing the food FR from 100 to 300 shifted the cocaine choice dose-response curve to the left; decreasing the cocaine FR from 10 to 1 also shifted the baseline cocaine choice dose-response curve to the left. In both environmental manipulations, phenmetrazine produced rightward shifts in cocaine choice dose-response curves. These findings highlight the interactions between contingencies and effectiveness of a potential candidate pharmacotherapy. Overall, these results suggest that agonist-based medications, such as phenmetrazine, might be most effective under contingencies that engender low unit cocaine dose choice and least effective under contingencies that engender high unit cocaine dose choice.

2.B. Imaging studies of cocaine self-administration

As mentioned earlier, nonhuman primate models of cocaine abuse have been used in combination with in vivo PET imaging to characterize trait variables associated with vulnerability (e.g., Howell et al., 2001, 2002; Morgan et al., 2002; Nader et al., 2006) and to examine how chronic cocaine self-administration alters brain function (e.g., Nader et al., 2006; Banks et al., 2008; Howell et al., 2010; Gould et al., 2011). There are recent reviews on this topic (Gould et al., 2012, 2013), so this section will only focus on issues related to the behavioral effects of cocaine under concurrent access conditions described in the previous section.

It was noted that access conditions altered cocaine choice and sensitivity to drug treatments (Banks et al., 2013). There is an important translational component to this observation – Volkow et al. (1993) noted that in cocaine abusers, it was years of use, not amount of cocaine being used, that was related to DA D2-like receptor binding potentials, as determined with PET imaging. Said another way, it appears that environmental variables may have a significant impact on DA receptor function, which could be a mechanism accounting for the effects of phenmetrazine reported by Banks and colleagues (2013).

Different schedules of cocaine availability (i.e., the use of different schedules of reinforcement for self-administration) when combined with PET imaging can provide important information related to the neuronal response to cocaine and how the behaviors leading to cocaine administration impact brain function. In one study (Nader et al., 2006), PET scans measuring DA D2-like receptor availability were conducted before and after male rhesus monkeys self-administered cocaine under a fixed-interval (FI) 3-min schedule of reinforcement. Approximately 1 month of cocaine self-administration resulted in an average 16% reduction in D2-like receptor availability (Nader et al., 2006). To determine whether this was due to cumulative cocaine intake (which was approximately 90 mg/kg) or to the monkeys having access to cocaine for 1 month, another group of cocaine-naïve monkeys was scanned before and after access to cocaine (0.03 mg/kg per injection) under an FI 30-min schedule of reinforcement (Czoty et al., 2007). For these studies, monkeys received 2 injections per session; when rescanned after 1 month of cocaine self-administration, DA D2-like receptor availability was not significantly different from baseline in any monkey, suggesting that at least initially, the reductions in DA D2-like receptor availability noted in the earlier study (Nader et al., 2006) were due to the pharmacology of cocaine, not to the behavior leading to cocaine administration.

A long history of cocaine self-administration robustly decreases DA D2-like receptor availability in monkeys (Nader et al., 2006) and humans (Volkow et al., 1993; Martinez et al., 2004). This history also changes DA D3 receptor availability (e.g., Staley and Mash, 1996), DA transporters (e.g., Letchworth et al., 2001), and other monoamine systems (e.g.,

Banks et al., 2008). This is one reason why testing a cocaine "antagonist" in animals with minimal cocaine history may not provide predictive information related to pharmacotherapy effectiveness. The monkeys in the Banks et al. (2013) study were well-trained and had extensive experience self-administering cocaine, so future studies should examine how changes in availability alter DA receptor function in monkeys with a long, high dose, cocaine history. Such information will be valuable for developing novel treatment strategies for cocaine addiction.

3. Social rank in nonhuman primate models

While drug abuse frequently occurs in a social context, very few animal studies (including the use of nonhuman primates) incorporate social context into the experimental design (see Nader et al., 2012a). For Old World macaques, social hierarchies are formed by outcomes of agonist interactions, with winners of fights being dominant to losers (Kaplan et al., 1982). Social hierarchies can be viewed as representing two ends of a continuum incorporating environmental enrichment for the dominant animals and socially derived stress for the subordinate animals (see Nader et al., 2012a for further discussion). As briefly described below, these socially derived environmental conditions can profoundly affect the behavioral consequences and neuropharmacology of drugs. As mentioned earlier, social rank can be considered an organismal or host variable – a drug effect may be different in a dominant vs. a subordinate monkey. However, since this review is focused on environmental variables, we consider dominant and subordinate ranks as a consequence of the social environment.

3.A. Social hierarchy and cocaine self-administration

Previous studies in socially-housed male monkeys found that subordinate animals self-administered cocaine at higher rates and greater intakes than dominant monkeys when cocaine was available under an FR schedule of reinforcement (Morgan et al., 2002). In fact, cocaine did not function as a reinforcer in dominant monkeys (i.e., response rates across all cocaine doses was not different than response rates when saline was self-administered). Such an outcome (cocaine not showing reinforcing effects at any dose) is rare in nonhuman primate studies using FR schedules of reinforcement. However, continued exposure to cocaine resulted in cocaine functioning as a reinforcer in dominant animals and response rates becoming similar between dominant-, intermediate- and subordinate-ranked monkeys (Czoty et al., 2004). An interesting possibility that requires additional research is whether dominant monkeys were initially more sensitive to the rate-decreasing effects of cocaine and that tolerance developed to those effects, resulting in the drug now functioning as a reinforcer. Changing the conditions from a simple FR schedule of reinforcement to a concurrent schedule resulted in a return to greater sensitivity to cocaine reinforcement in subordinate monkeys (Czoty et al., 2005a). Thus, differences between social ranks re-emerged under conditions in which the environmental context was changed.

Several studies have used cocaine-food choice paradigms to study the influence of social rank on environmental and pharmacological manipulations on cocaine self-administration in monkeys (Czoty and Nader, 2012, 2013; see Nader et al., 2012a for recent review). Understanding how environmental or pharmacological variables differentially affect cocaine choice in dominant and subordinate monkeys can provide insight into mechanisms mediating these rank-related differences. For example, most research from our group has focused on DA receptor function (see below), but what about serotonin (5-HT) neurotransmission? Czoty et al. (2005b) examined the effects of 8-OH-DPAT, a 5-HT1A agonist, on cocaine-food choice in dominant and subordinate monkeys and found (1) that 8-OH-DPAT increased cocaine choice at the lower doses and (2) there were no rank-related differences, indirectly suggesting that 5-HT1A receptors are not differentially affected by social context. In a more recent study, social rank-related differences in the ability of high-

and low-efficacy DA D2 receptor agonists were noted (Czoty and Nader, 2013), supporting a prominent interaction between D2 receptors and social rank related to rates of cocaine self-administration.

Individual differences are a hallmark of drug addiction. Socially housed monkeys responding under cocaine-food choice paradigms provide a means to systematically examine these individual subject differences (Nader et al., 2012a). As it relates to environmental variables, it can be hypothesized that environmental stressors should shift the cocaine dose-response curve to the left, while environmental enrichers should shift the cocaine curve to the right. However, what stimulus is enriching or stressful cannot be determined in the absence of behavior – this same premise has existed in the area of experimental analysis of behavior for decades (e.g., Barrett and Glowa, 1977; Spealman, 1979). As it relates to between-subject variability, Czoty and Nader (2012) found that the same manipulation, whether it was moving monkeys to a larger pen (hypothesized to be enriching) or introducing a toy snake (hypothesized to be stressful), not all dominant and subordinate monkeys responded in the same manner (i.e., shifts in the cocaine dose-response curve). Such information is valuable in phenotypically characterizing each monkey. With the combination of behavioral pharmacology and in vivo brain imaging, future studies may be able to determine why a toy snake shifted the cocaine dose-response curve to the left in a subordinate monkey and had no effect or rightward shift in another subordinate animal. When compared to drug treatment effects, such phenotypic information may provide insight into future treatment responders and non-responders.

3.B. Imaging studies of social behavior

PET imaging studies indicate that the initial differences noted in the reinforcing effects of cocaine between dominant and subordinate male monkeys may be related to DA D2-like receptor availability. Morgan et al. (2002) noted that prior to initiating cocaine self-administration studies, PET studies indicated that dominant male monkeys had an approximately 20% higher D2-like receptor availability compared to subordinate male monkeys. Volkow et al. (1999b) noted that there appears to be an inverse relationship between D2-like receptor measures a psychomotor stimulant reinforcement (methylphenidate in that study) – subjects with low D2-like receptor binding potentials found methylphenidate more pleasant than subjects with high D2-like receptor availability. Since the Volkow et al. (1999b) and Morgan et al. (2002) studies, others (Nader et al., 2006; Dalley et al., 2007) have noted a similar inverse relationship between D2-like receptor availability and cocaine reinforcement.

There are several important facets of these findings. First, it appears that DA D2-like receptor availability may be a trait variable that influences vulnerability. Secondly, these receptor measures appear quite malleable to environmental, social and pharmacological manipulations. Thirdly, and perhaps most importantly, most of the studies examining the relationship between cocaine reinforcement and D2-like receptor availability have involved male subjects. A recent study attempted to replicate and extend the findings of Morgan et al. (2002) to socially housed female monkeys (Nader et al., 2012b). DA D2-like receptor availability changed in female monkeys that became dominant, just as was noted in male monkeys. Importantly though, the dominant female monkeys were more vulnerable to cocaine reinforcement, in contrast to the dominant male monkeys which were initially protected from the reinforcing effects of cocaine. These findings suggest the interesting possibility that the relationship between D2-like receptor availability and cocaine reinforcement may be opposite in males and females, although much additional work is needed.

The behavioral studies described above in socially housed male monkeys also showed that social rank could impact cocaine-food choice. As it relates to the behavioral observations noted – subordinate male monkeys were more sensitive to the reinforcing effects of cocaine compared to dominant monkeys (Czoty et al., 2005a) – this cannot be mechanistically explained by DA D2-like receptor differences. In fact, in well-established social groups of male monkeys with an extensive cocaine history, there are no statistically significant differences in D2-like receptor availability (Czoty et al., 2004). However, that does not mean that social variables are not impacting brain function, only that DA D2-like receptor availability is not different. A particular advantage of nonhuman primate studies is the ability to assess multiple targets over many years to more fully characterize individual trait and state markers associated with vulnerability and maintenance of cocaine use. This should be an objective of future research, as well as the study of sex differences in response to chronic drug exposure.

4. Punishment of cocaine self-administration

By definition, punishment is a reduction in the probability that a specific behavior will occur as a result of the consequence of that behavior (Azrin and Holz, 1966). The process is called punishment, and the consequence event, the stimulus, is the punisher. There are two broad types of punishment. Positive punishment is a reduction in behavior because that behavior resulted in the presentation of a stimulus event. In preclinical research that stimulus is most frequently an electric shock. As it relates to drug abuse, disulfiram (Antabuse®) for the treatment of alcoholism is based on the principles of positive punishment. Negative punishment results in a decrease in behavior because the consequence of that behavior is the removal of a (most likely reinforcing) stimulus. Response-contingent timeout from a reinforcer is an example of negative punishment. As it relates to human drug abuse, incarceration could be considered an example of negative punishment (although some may argue that what happens in prison could be considered positive punishment). It was our goal in this review to directly compare the efficacy of punishment and reinforcing alternative behaviors, but this has turned out to be very difficult primarily because it is impossible to equate magnitude of a punisher with magnitude of a positive reinforcer. For the purposes of this review, we highlight some of the research on positive and negative punishment and their effects on cocaine self-administration and describe the large gaps in knowledge related to brain mechanisms mediating these effects.

4.A. Behavioral effects of punishment

Grove and Schuster (1974) were the first to examine positive punishment on cocaine self-administration in monkeys. For these studies, four experimentally naïve male rhesus monkeys were trained to self-administer cocaine under a multiple (mult) FR 1 schedule of reinforcement in which cocaine (0.1 mg/kg per injection) was available in both components; these components were 30 min in duration and cycled three times each session (total of 3 hrs). First, they examined the effects of extinction conditions (responding had no programmed consequence) in the second component and found that while responding declined in that component, there were transitory increases in responding in the first component. Such an effect has been reported in pigeons responding under multiple schedules involving food reinforcement and is referred to as "behavioral contrast" (Reynolds, 1961). When the conditions were changed to a mult FR1 cocaine, FR1 cocaine + shock (punishment), responding in component 2 decreased in a shock-intensity dependent fashion, as hypothesized. There was evidence of behavioral contrast (increases in cocaine self-administration) in the non-punished component, but it was described as transitory. Increasing the cocaine dose from 0.1 to 0.2 mg/kg per injection did not attenuate the punishing effects of shock. This study suggested that cocaine self-administration could be punished using environmental manipulations.

A more systematic examination of the effects of positive punishment on cocaine self-administration in rhesus monkeys did not observe such promising reductions in drug-maintained behavior. Bergman and Johanson (1981) trained rhesus monkeys to self-administered cocaine under an FR 10 schedule of reinforcement and found that intermediate shock intensities would initially decrease responding, but the punishing effects of the shock dissipated with continued exposure. Only when high intensity shocks were used did responding remain suppressed. However, when the shock contingency was removed, cocaine self-administration returned to baseline values or higher. In another study, Johanson (1977) used a discrete-trials choice procedure and found that increasing the dose of cocaine available could reverse the suppressant effects of shock. Thus, while Grove and Schuster did not observe an attenuation of punishment with increasing doses, changing the schedule contingencies to a choice paradigm resulted in a completely different interpretation of the qualitative effects of punishing cocaine self-administration. The effects of punishing cocaine self-administration in the context of alternative non-drug reinforcers results in reallocation of responding to the food choice (Negus, 2005). Parametric studies involving different magnitudes of food reinforcers have not yet been conducted, but it is likely that these conditions would (1) require lower intensities of the punisher and (2) produce qualitatively greater reductions in cocaine self-administration. It would be interesting to conduct this study and test the animals with clinically effective anxiolytics – drugs that have been shown to increase punished responding (see Barrett, 1992).

Other investigators have used drugs as the positive punisher. Goldberg (1980) trained squirrel monkeys under a mult FR 30 schedule of food presentation; components cycled five times per session. Response-contingent injections of histamine (0.03–0.1 mg/kg, i.v.) suppressed food-maintained responding by up to 80% of baseline. In one monkey (S-18) there was evidence of behavioral contrast – unpunished responding increased when histamine suppressed responding in the other component. As with electric shock-suppressed responding, behavior suppressed by histamine could be reversed by administration of the anxiolytics chlordiazepoxide and pentobarbital (Goldberg, 1980; but see Branch et al., 1977).

The use of histamine to punish food-maintained responding in the context of a choice paradigm was later shown by Woolverton (2003). In that study, rhesus monkeys responded under a concurrent variable-ratio (VR) 10 schedule of food presentation (two 1.0-g banana-flavored pellets). Responding on one lever was associated with food pellets and an i.v. injection of saline, while responding on the other lever (under the identical VR 10 schedule of reinforcement) was associated with food pellets and an i.v. injection of histamine. For comparison, later studies used cocaine injections as the consequent stimulus instead of histamine. Histamine punished choice responding; the lowest effective dose was 0.0015–0.006 mg/kg, which was substantially more potent than what was reported by Goldberg (1980) and Katz and Goldberg (1986) in squirrel monkeys (0.03–0.1 mg/kg histamine). In contrast to the effects observed with histamine, Woolverton (2003) found that if cocaine was substituted for histamine, monkeys chose the food + cocaine option more times than the food + saline alternative, providing clear support for histamine functioning as a punisher. These results highlight the importance of schedule contingencies and other programmed consequences on the potency and efficacy of drugs or other stimuli to function as punishers.

While positive punishment has been more commonly used in animal models, it is negative punishment that is most often implemented for dealing with human drug abusers. If the drug abuser is a professional, drug use could be punished by removing an important commodity, such as their professional license (Crowley, 1984). The most frequent example of negative punishment is incarceration. Nader and Morgan (2001) examined negative punishment contingencies in rhesus monkeys trained to self-administer cocaine under a multiple fixed-

interval (FI) 5-min schedule of reinforcement. Responding in one component was punished and the negative punisher was response-contingent timeouts (TO; 0–60-s), with TOs contingent on responding under a variable-interval (VI) 30-s schedule of reinforcement. The final contingency was a mult FI 5-min cocaine, conjoint (FI 5-min cocaine, VI 30-s TO) schedule of reinforcement (conjoint means that both schedules were operating simultaneously and independent of each other). The investigators reported that response-contingent TO decreased cocaine self-administration and that responding in the unpunished component did not increase (i.e., no behavioral contrast). However, as was noted in all other cases of punishment, there was little evidence of the punisher generalizing to other conditions. That is, not all cocaine self-administration was suppressed, only responding in the conjoint component of the multiple schedule of reinforcement and when the response-contingent TO was removed, self-administration returned to baseline.

4.B. Imaging studies of punishment

Woolverton (2003) concluded that a better understanding of the behavioral pharmacology of drugs that function as punishers might provide insight into the neurobiological mechanisms mediating drug self-administration. Unfortunately, there are no published preclinical studies using imaging techniques to elucidate the neurobiological mechanisms of different stimuli (electrical shock or intravenous histamine) that function as punishers. For example, previous research using in vivo PET imaging has established that drugs that function as reinforcers also decrease the binding potential of the DA D2-like radiotracer raclopride in both animals and humans by increasing synaptic DA levels (Volkow et al., 1993, 1999a; Martinez et al., 2007). A potential research question might be to determine if intravenous histamine administration produced a decrease in synaptic dopamine levels and a corresponding increase in raclopride binding potential. Furthermore, there are also no published studies determining the neurobiological interactions between reinforcing and punishing stimuli. Again, would intravenous histamine administration attenuate cocaine-induced increases in synaptic DA levels as measured with PET? We believe determining the neurobiological effects of stimuli that function as punishers is critically needed to further our knowledge of the environmental determinants of drug self-administration in animal models of drug addiction.

Although there are no published preclinical imaging studies of punishment, a recent human laboratory study of punished behavior and corresponding PET imaging can provide a conceptual framework for a future direction of both preclinical imaging and operant behavioral studies (see next section: Future Directions). In healthy subjects, measures of DA biosynthesis using the PET ligand [^{18}F]fluoro-L-m-tyrosine were correlated with performance on a reversal learning cognitive behavioral task (Cools et al., 2009). Specifically, individuals with high DA synthesis as measured with PET performed better after reinforcement-based versus punishment-based reversal learning, whereas individuals with low DA synthesis measures performed better after punishment-based versus reinforcement-based reversal learning. We posit that preclinical studies, in general, and nonhuman primates in particular, are well positioned to elucidate the neurobiological mechanisms of punishment and correlating neurobiological effects with behavior using both traditional operant schedules and other schedules of reinforcement used to interrogate cognition.

5. Future Directions

The goal of this review was to highlight environmental variables mediating cocaine abuse in nonhuman primate models and to describe in vivo imaging studies to elucidate potential mechanisms of action for these various environmental variables. Ultimately, we were interested in whether different environmental variables (e.g., punishment vs. alternative

reinforcers) could be described in relation to similar CNS mechanisms of action. This proved difficult because no imaging work has been done in nonhuman primates related to punishment of drug taking. We highlighted the importance of combining brain imaging with behavior – a hallmark of behavior pharmacology is the appreciation of environmental context, experimental history, and the fact that a stimulus cannot be described as reinforcing or punishing in the absence of behavior. Studying brain mechanisms without behavior is incomplete and potentially misleading. The use of nonhuman primates allows for the study of individual differences in a longitudinal manner – within-subject analyses over many years. As highlighted in this review, future work is needed that directly compares males and females. Female Old World macaques have a 28-day menstrual cycle that has been shown to influence DA D2-like receptor availability (Czoty et al., 2009), making them ideally suited as a preclinical model for understanding the neuropharmacology of cocaine abuse in women. Clearly, much additional research involving female monkeys is required in order to develop individualized treatment strategies.

Other advantages to using nonhuman primates include the ability to study cognitive behaviors and correlate these behavioral changes with brain imaging measures of glucose metabolism and receptor changes (e.g., Gould et al., 2012, 2013). For example, if an environmental manipulation decreases cocaine choice in monkeys, but does not reverse cognitive impairments on cognitive behavioral tasks associated with that cocaine history, these results suggest a combination of drug treatments may be necessary, since it has been hypothesized that cognitive impairments have impeded treatment success (Aharonovich et al., 2006; Turner et al., 2009; Moeller et al., 2010). Thus, the combination of brain imaging techniques with multiple behavioral endpoints should provide a template on which to further understand the neuropharmacological consequences of long-term cocaine abuse and allow for a better assessment of treatment strategies for cocaine addiction in preclinical models.

Acknowledgments

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Highlights

- Nonhuman primate PET imaging is translational science

- Alternative reinforcers and punishment can decreases drug use; only the former has been studied with imaging

- The social environment can impact cocaine taking and brain function

- There is clinical potential in monkey models of cocaine reinforcement and imaging