Review

Positron emission tomography imaging studies of dopamine receptors in primate models of addiction

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Animal models have provided valuable information related to trait and state variables associated with vulnerability to drug addiction. Our brain imaging studies in monkeys have implicated D₂ receptors in cocaine addiction. For example, an inverse relationship between D₂ receptor availability and rates of cocaine self-administration has been documented. Moreover, environmental variables, such as those associated with formation of the social hierarchy, can impact receptor availability and sensitivity to the abuse-related effects of cocaine. Similarly, both D₂ receptor availability and cocaine self-administration can be altered by chronic drug administration and fluctuations in hormone levels. In addition, cocaine self-administration can be altered in an orderly fashion by presentation of an acute stressor, such as acting as an intruder into an unfamiliar social group, which can shift the cocaine dose–response curve to the left in subordinate monkeys and to the right in dominant animals, suggesting an interaction between social variables and acute stressors. Conversely, irrespective of social rank, acute environmental enrichment, such as increasing the size of the living space, shifts the cocaine dose–response curve to the right. These findings highlight a pervasive influence of the environment in modifying the reinforcing effects of cocaine and strongly implicate brain D₂ receptors.

Keywords: dopamine; D₂ receptors; cocaine self-administration; social behaviour; animal models; non-human primates

1. INTRODUCTION

Drug abuse continues to be a major public health problem worldwide (WHO 2004). In the USA, approximately 2.9 million persons aged 12 or older used an illicit drug for the first time in 2005, with recent estimates of 2.4 million Americans confirming current cocaine use (SAMHSA 2006). Within the European Union, lifetime experience with cocaine for 15–24 year old males was reported at 5–13% (WHO 2004). In 2001, 56% of all countries reporting on cocaine trends reported increases; in Europe, the number was 67% (WHO 2004). At present there are no medically approved treatments for cocaine addiction, although several novel pharmacological avenues are being considered (e.g. O'Brien 2005; Elkashef *et al.* 2007). The overarching goal of the research programme described in this review is to examine behavioural, pharmacological and neurochemical correlates of vulnerability, maintenance and relapse to cocaine addiction in non-human primate models. This research strategy holds the premise that a better understanding of these variables may lead to improved treatment strategies for cocaine addiction.

As pointed out by James Mills in 1965, '[A]ny disease—including drug addiction—depends for its spread on the three necessities: a susceptible individual,

an infecting substance and an environment where the two can meet'. More recently, these 'necessities' have been described in terms of the 'agent', the 'host' and the 'context' (O'Brien 2006). In this review, we will describe how these three variables are considered in the development of novel treatment strategies for cocaine abuse. While we focus on cocaine, it is our hypothesis that these strategies, which emphasize the social context and environmental conditions, are relevant for all drugs of abuse.

(a) *The agent*

Cocaine is an indirect-acting monoamine agonist, which binds with approximately equal affinity at the dopamine (DA), serotonin (5-HT) and noradrenaline transporters (Ritz *et al.* 1987; Woolverton & Johnson 1992). The vast majority of studies on the mechanisms of action mediating the high abuse liability of cocaine focus on the DA system. Briefly, DA cells from the ventral tegmental area project to structures within the striatum, including the nucleus accumbens, and project to the cortex (Haber & McFarland 1999); these pathways have been implicated in all rewarding behaviours (Di Chiara & Imperato 1988). DA released into the synapse is primarily removed by active uptake by the DA transporter. Cocaine acts by blocking the transporter and elevating the levels of extracellular DA, which produces its downstream effects by binding to two superfamilies of DA receptors, D₁- and D₂-like receptors (Sibley *et al.* 1993). The imaging work

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described in this review will focus on D₂-like receptors and imaging tools, [¹¹C]raclopride and [¹⁸F]fluorocleobopride (FCP), that do not differentiate among the subtypes of the D₂ superfamily (Mach *et al.* 1993). Also of relevance is whether the D₂ positron emission tomography (PET) ligands are assessing pre- or postsynaptic D₂-like receptors. Based on lesioning work (Chalon *et al.* 1999), we hypothesize that changes in D₂ receptor availability are primarily due to changes in postsynaptic D₂ receptor function (see Nader & Czoty 2005).

Research into the pharmacodynamics and pharmacokinetics of cocaine that leads to its high abuse potential has enhanced our understanding of the DA system and reward mechanisms. Using techniques such as *in vivo* microdialysis in animals surgically implanted with cannulae targeting various brain structures, cocaine has been shown to elevate levels of extracellular DA in areas of the brain that are believed to mediate reinforcement (see Bradberry 2000; Czoty *et al.* 2002; Howell & Wilcox 2002). In humans, using non-invasive brain imaging techniques such as PET, the relationship between elevating DA and subjective drug effects was examined (Volkow *et al.* 1999). In that study, investigators administered [¹¹C]raclopride, which binds to postsynaptic DA-D₂ receptors, and measured the displacement of that radiotracer by DA in non-drug abusing individuals. Because cocaine could not be administered to these individuals for ethical reasons, the investigators used another indirect-acting DA agonist, methylphenidate, that has reinforcing effects in animals and humans (e.g. Johanson & Schuster 1975; Volkow *et al.* 1999). There was an orderly relationship between the ability of methylphenidate to elevate DA and displace [¹¹C]raclopride from D₂-like receptors and the intensity of the subjective reports of 'high'. Importantly, in the subjects that did not report a high, methylphenidate did not elevate DA.

Finally, despite the clear relevance of specific actions of cocaine at neurobiological target sites, it is important to point out that it is our premise that the prominent abuse-related effects of cocaine are not simply explained by pharmacological interactions between drug and receptor. There are clearly profound differences in the behavioural effects of cocaine when administered non-contingently by the investigator versus self-administered by the animal (Dworkin *et al.* 1995; Stefanski *et al.* 1999; Bradberry 2000). Moreover, as described in detail below, the schedule of cocaine availability can have profound effects on the CNS consequences of cocaine exposure.

(b) *The host*

The studies described below used non-human primates, specifically, rhesus monkeys (*Macaca mulatta*) or cynomolgus monkeys (*Macaca fascicularis*). Along with baboons, these Old World monkeys are the most closely phylogenetically related species to humans that can be used in biomedical research. Thus, our ability to accurately generalize from laboratory animal models to human drug abuse is enhanced by using monkeys as subjects; this is particularly important for imaging studies (Nader & Czoty 2008). There are

documented differences between monkey and rodent dopaminergic systems (Berger *et al.* 1991; Joel & Weiner 2000), including differences in DA affinity at D₁- and D₂-like receptors (Weed *et al.* 1998), as well as evidence of species differences in cocaine-induced changes in brain function (e.g. Lyons *et al.* 1996) and in the behavioural effects of indirect-acting DA agonists including cocaine (e.g. Roberts *et al.* 1999; Lile *et al.* 2003). There are also data indicating that many drugs, including drugs of abuse, have similar pharmacokinetic profiles in monkeys and humans, which differ in rodents (e.g. Banks *et al.* 2007; see Weerts *et al.* 2007 for review).

Monkeys also allow for the investigation of social variables in cocaine abuse (Morgan *et al.* 2002; Czoty *et al.* 2005); these studies provide a unique translational component to our research. The social hierarchy (i.e. the social ranks of each of the four monkeys in a group) is determined by recording winners of fights between the monkeys (Kaplan *et al.* 1982). The first-ranking ('dominant') monkey is defined as the monkey that wins fights against the other three monkeys. The second-ranking monkey wins all fights except against the first-ranking monkey, and so on. The monkey that loses fights with all others in the pen is designated the lowest-ranking ('subordinate') monkey.

Sex is a host factor that has been largely overlooked in drug abuse research. While the majority of our research has focused on male subjects, there is growing evidence for sex differences in behaviour, pharmacology and neurochemical actions of abused drugs (Lynch *et al.* 2002; Lynch 2006; Turner & de Wit 2006). Importantly, these reported sex differences extend beyond drug abuse to include most psychiatric disorders including schizophrenia, Parkinson's disease and obsessive-compulsive disorder (e.g. Seeman 1996; Wieck *et al.* 2003). In female subjects, there is evidence that menstrual cycle phase can alter sensitivity to drugs of abuse (see Turner & de Wit 2006). Female macaques have an approximately 28-day menstrual cycle, with fluctuations in oestrogen and progesterone resembling those of women (e.g. Jewitt & Dukelow 1972; Appt 2004), making them ideal for studying conditions related to women's health. Although not discussed in this paper, studies related to prenatal drug exposure would also benefit from the use of non-human primates. For example, the gestation period in macaques is approximately six months, which is close to human gestation and much longer than rodent models (Sandberg & Olsen 1991).

Of relevance to the topic of this review, we recently investigated how menstrual cycle phase influenced measures of DA-D₂ receptor availability in female cynomolgus monkeys (Czoty *et al.* 2008). As will be described below, there appears to be a relationship between D₂ receptor availability and reinforcing effects of cocaine. Thus, if menstrual cycle phase influences D₂ receptor levels, this may be a primary mechanism for differences in abuse-related effects of cocaine (or other abused drugs) in women tested at different times of the month (Sofuoglu *et al.* 1999). Three PET imaging studies in women have investigated D₂ receptor availability as a function of menstrual cycle; three different outcomes were reported. Wong *et al.* (1988)

reported a trend towards lower radiotracer uptake in the striatum of women tested in the follicular versus luteal phase. In a more recent study, they found lower D₂ receptor measures in the putamen (but not caudate nucleus or ventral striatum) in women in the luteal versus follicular phase (Munro *et al.* 2006). Finally, Nordstrom *et al.* (1998) found no evidence of menstrual cycle-dependent variations in D₂ receptor availability in the putamen in five women. Several factors could account for these disparate results, including the stress level and the drug history of the women. Importantly, these factors can be controlled in animal studies. In seven experimentally naive, normally cycling female cynomolgus monkeys, we found that D₂ receptor availability was significantly (approx. 13%) lower in the follicular phase compared with the same monkeys studied during the luteal phase (Czoty *et al.* 2008). Such an outcome supports differences in sensitivity to drug effects at various stages of the menstrual cycle and underscores the importance of the hormonal milieu as a host factor that may influence the effects of abused drugs. Moreover, these data suggest that studies in female subjects should minimize the influence of menstrual cycle fluctuations by taking measurements in the same menstrual cycle phase when conducting longitudinal studies.

(c) *The context*

In our studies, we view the context as encompassing all environmental stimuli, experimental history and social status. For this paper, we will limit the context to a brief description of models used to assess cocaine reinforcement and to non-human primate social behaviour. When describing the models of drug self-administration with respect to the schedule of reinforcement, an important distinction should be made between reinforcing 'effects' and reinforcing 'strength'. A reinforcing effect simply means that responding leading to drug presentation occurs at higher rates than responding leading to vehicle presentation. For every drug that has reinforcing effects, the shape of the dose–response curve approximates an inverted U-shape. That is, there is an ascending limb characterized by dose-dependent increases in responding, a dose that results in peak rates of responding and a descending limb in which increases in dose result in lower rates of responding (see Zernig *et al.* 2004). Because several factors influence the shape of the curve, it is impossible to compare dose–response curves from different drugs and make statements related to which drug is 'more reinforcing' (Woolverton & Nader 1990). However, other schedules can be used to make assessments related to reinforcing strength; these will be described in more detail below. The main point to highlight is that different schedules of reinforcement have features that render them suitable for answering different questions about the behavioural effects of cocaine. For example, questions related to the relative importance of drug seeking (i.e. simply self-administering cocaine) versus total cocaine intake in producing changes in the brain can be assessed by studying different schedules of cocaine self-administration. Such a distinction is

of clear relevance when considering treatment options for drug abuse—does it matter how much drug a patient has taken or how long (s)he has been abusing the drug? Volkow *et al.* (1999) found that levels of DA-D₂ receptor availability as measured with PET were more dependent on the duration of cocaine use than on the amount of drug used prior to the study. This finding suggested that the behaviours leading to drug procurement, independent of the pharmacology of cocaine, could contribute to the reported changes in DA receptor availability in cocaine abusers and supported the hypothesis that the environment can have profound effects on the brain.

The use of non-human primates, PET imaging and different schedules of reinforcement provided an opportunity to directly assess the importance of drug seeking versus total cocaine intake (Czoty *et al.* 2007a,b). To directly test this hypothesis, 12 experimentally naive rhesus monkeys received baseline PET scans using the D₂ receptor ligand [¹⁸F]FCP. Six of these monkeys were then trained to self-administer cocaine under a second-order schedule, a very lean schedule of reinforcement in which drug seeking was maintained by the presentation of conditioned stimuli throughout the 60 min session until cocaine was finally administered (Katz 1980). Under the final schedule parameters, the first response after 3 min (fixed interval; FI 3 min) produced a stimulus change (S) associated with cocaine reinforcement and the tenth completed FI (i.e. fixed ratio 10) resulted in cocaine presentation (designated FR 10 [FI 3 min:S]). Sessions ended after two cocaine injections (0.1 mg kg⁻¹ injection⁻¹). Thus, these animals had an extensive drug-seeking history, but very low levels of cocaine intake. The second group of six monkeys was trained to respond under an FR 30 schedule of cocaine presentation. Conditions for this group were arranged to model 'binge' access—monkeys could receive up to 30 injections of 0.3 mg kg⁻¹ cocaine twice per day, 2 days per week. Thus, relative to the other group of monkeys, this set of subjects received much more cocaine but drug seeking was only 2 days per week. We found that binge access to cocaine resulted in significant reductions in D₂ receptor availability at every time point, while 'drug seeking' under the second-order schedule did not significantly affect D₂ receptor availability over 1 year. These findings suggest that the reductions in D₂ availability seen in humans were primarily due to the direct effects of cocaine on DA receptor levels.

(i) *Organism × environment interactions: part 1*

Acquisition of drug reinforcement is influenced by characteristics of the individual (i.e. trait variables) as well as by features of the environment (e.g. state variables). One of the first studies of the relationship of trait variables to sensitivity to drug reinforcement was provided by Piazza *et al.* (1989) in which two groups of rats were differentiated based on locomotor activity in an open-field apparatus as high responders (HR) or low responders (LR). Rats were implanted with indwelling intravenous catheters and given access to low doses of *d*-amphetamine under an FR schedule. HR rats acquired *d*-amphetamine self-administration at lower

doses than LR rats. The use of this simple schedule allowed for characterization of vulnerability based on an inherent behavioural characteristic, namely, locomotor activity in an open field.

More recently, laboratory animal studies have examined behaviours related to 'impulsivity', a trait shown to be high in cocaine abusers (Moeller *et al.* 2002). Rats characterized as more impulsive acquired cocaine self-administration more rapidly than less impulsive rats (Dalley *et al.* 2007). Perry *et al.* (2005) addressed whether impulsivity precedes drug abuse. In that study, rats were trained on a delay discounting procedure in which responding on one lever under an FR 1 contingency resulted in the immediate delivery of one food pellet, while responding on another lever under an FR 1 contingency resulted in the delivery of three food pellets after a variable delay. If the rat chose the immediate option, the delay value decreased on the next trial for the alternative; if the delay option was chosen, the delay value increased on the next trial. A mean adjusted delay (MAD) value was calculated for each rat by averaging all delay values across trials. As described by Perry *et al.* (2005), the MAD served as a quantitative measure of the extent to which each rat discounted delayed food reinforcers. Higher MAD values, representing longer delays, were indicative of low impulsivity, while smaller MAD values indicated more impulsive behaviour. The rats were divided into two groups, high and low impulsiveness (HiI and LoI, respectively) based on MAD values. When cocaine acquisition was studied, HiI animals acquired self-administration more rapidly and at higher levels than LoI rats. Taken together, these findings support the hypothesis that there are behavioural traits that predispose individuals to drug abuse and these can be examined using animal models.

Our group has studied trait variables and gene-environment interactions in relation to drug abuse in non-human primates for over a decade. Much of our research has been conducted in cocaine-naïve monkeys prior to being exposed to cocaine in order to address gaps in the clinical data—questions that cannot be answered in humans due to ethical concerns. For example, as described above, cocaine abusers have lower levels of D₂ receptor availability than control subjects (Volkow *et al.* 1990, 1993; Martinez *et al.* 2004) and non-drug abusers with lower basal levels of D₂ receptor availability found methylphenidate more reinforcing (Volkow *et al.* 1999). It is not known whether low D₂ levels were the result of cocaine use or a pre-existing feature that conferred vulnerability to the reinforcing effect of cocaine. The question is whether D₂ receptor availability is a trait marker for vulnerability to cocaine abuse. We have directly addressed this question in two ways. First, we correlated basal D₂ receptor availability in cocaine-naïve monkeys with subsequent rates of cocaine self-administration. Second, we studied the changes in D₂ receptor availability in cocaine-naïve monkeys over 1 year of access to determine whether cocaine reinforcement decreased these levels (Nader *et al.* 2006). A summary of the findings is shown in figure 1. Initially, cocaine-naïve monkeys were scanned with the D₂ receptor

ligand [¹⁸F]FCP and then trained to respond under an FI 3 min schedule of food presentation. When responding was stable, each monkey was surgically implanted with an indwelling venous catheter, a dose of cocaine (0.2 mg kg⁻¹ injection⁻¹) was substituted for food and response rates were recorded. An important point is that there was no training under the cocaine self-administration paradigm—the monkeys were simply exposed to the drug and response rates were recorded. We found an inverse relationship between baseline D₂ receptor availability and the rates of cocaine self-administration (figure 1a). Monkeys with low D₂ receptor levels self-administered cocaine at higher rates compared with monkeys with high D₂ receptor availability. These findings are very similar to the observations by Volkow *et al.* (1999) using non-drug abusers and methylphenidate. We also found that, over a 1-year period in which cocaine intake increased steadily, D₂ receptor availability decreased irrespective of what the initial levels of D₂ receptor availability were for each monkey (figure 1b). Thus, it appears that low D₂ receptor availability makes an individual more vulnerable to cocaine reinforcement and continued exposure to cocaine further decreases those levels (Nader *et al.* 2002, 2006).

The above findings clearly support the idea that there are biological trait variables, in this case D₂ receptor availability, that influence vulnerability to cocaine abuse. We have also examined the impact of environmental variables on D₂ receptor availability and whether these effects influenced vulnerability to cocaine reinforcement. Earlier work from our group demonstrated a relationship between D₂ receptor availability and social rank in female monkeys, such that subordinate monkeys had lower D₂ receptor levels than dominant monkeys (Grant *et al.* 1998). We next assessed whether D₂ receptor availability was a trait variable that predicted social rank. For these studies, we used 20 experimentally naïve and individually housed male cynomolgus monkeys. After baseline PET scans using [¹⁸F]FCP were conducted, monkeys were placed in social groups of four monkeys per pen and after three months were rescanned with [¹⁸F]FCP (Morgan *et al.* 2002). D₂ receptor availability was not a trait marker for eventual social rank. After three months of social housing, we observed the same effect that was reported by Grant *et al.* (1998) in female monkeys that had been living together for over 3 years—subordinate monkeys had lower D₂ receptor availability compared with dominant monkeys. However, it came about in a manner opposite to what we had expected. We had hypothesized that the lower D₂ receptor levels in subordinate monkeys compared with dominant monkeys arose as the result of chronic social stress that is unequivocally experienced by subordinate monkeys (Kaplan *et al.* 1982; Shively & Kaplan 1984). However, the over 20% difference between dominant and subordinate monkeys in our study was due to a significant increase in D₂ receptor availability in dominant monkeys whereas subordinates, on average, did not change. These increases in D₂ measures were in the same direction as reported in rodent studies demonstrating the influence of environmental enrichment on DA function—including

Figure 1. (a) Correlation between baseline D_2 receptor availability and rates of cocaine self-administration in male rhesus monkeys. (b) Representative data from one monkey (R-1241) showing cumulative cocaine intake and associated changes in D_2 receptor availability. Adapted from Nader *et al.* (2006).

increased D_2 receptor densities (e.g. Bowling *et al.* 1993; Rilke *et al.* 1995; Hall *et al.* 1998). Based on these rodent studies and on our findings that there was an inverse relationship between D_2 receptor availability and cocaine self-administration, we hypothesized that the subordinate monkeys would self-administer more cocaine than the dominant monkeys. Our hypothesis was borne out (Morgan *et al.* 2002). In fact, cocaine was not a reinforcer in the dominant monkeys when assessed under an FR 50 schedule of reinforcement (see Nader & Czoty 2005 for additional discussion).

We also examined other behaviours that we hypothesized could be trait variables predictive of social rank. In our initial study (Morgan *et al.* 2000), locomotor activity predicted eventual social rank in that eventual subordinate monkeys had higher locomotor scores compared with eventual dominant monkeys; interestingly, this was not extended to female monkeys (Riddick *et al.* submitted). Most recently, we have extended our measures to include behaviours deemed to assess impulsivity in an effort to extend more recent work in rodents (e.g. Perry *et al.* 2005; Dalley *et al.* 2007). In a group of experimentally naive and individually housed female cynomolgus monkeys, we used a measure of novel object reactivity to assess impulsivity in each animal prior to being socially housed (Riddick *et al.* submitted). Monkeys that would eventually become subordinate had shorter latencies to approach the novel

object compared with eventual dominant female monkeys. Shorter latency is hypothesized to represent greater impulsivity. Whether the more impulsive monkeys are also more vulnerable to self-administer cocaine as was reported in rodents by Perry *et al.* (2005) and Dalley *et al.* (2007) is currently being evaluated.

(ii) Organism $\times$ environment interactions: part 2

In our socially housed male monkeys, we have extended earlier work in an effort to further enhance our homologous model of the human condition. These experiments primarily focus on changing environmental conditions. For example, we found that the protective effect associated with being the dominant monkey can be attenuated by continual exposure to cocaine (Czoty *et al.* 2004). That is, while there were differences in rates of self-administration when initially exposed to the FR 50 schedule (Morgan *et al.* 2002), repeated exposure to cocaine over a 1-year period resulted in cocaine becoming a reinforcer in dominant monkeys (see e.g. figure 2a). After several months to years of cocaine self-administration, neither response rates nor D_2 receptor availability were different in dominant compared with subordinate monkeys (Czoty *et al.* 2004). As mentioned above, simple schedules do not provide information related to reinforcing strength. Thus, we examined whether there would be differences between social ranks under conditions in which cocaine

Figure 2. (a) Cocaine dose–response curve in a dominant male monkey (C-5386). Filled circles (initial) were taken shortly after social hierarchies became stable (adapted from Morgan *et al.* 2002); open circles are the re-determined cocaine dose–response curve after approximately 1 year of self-administration (adapted from Czoty *et al.* 2004). (b) Cocaine–food choice data from dominant (circles) and subordinate (triangles) monkeys (Czoty *et al.* 2005). These data were acquired after the data shown in (a).

was available in the context of an alternative, non-drug reinforcer (Czoty *et al.* 2005). We found that subordinate monkeys were significantly more sensitive to the reinforcing effects of cocaine using this procedure, such that they would choose a lower dose of cocaine over food compared with dominant monkeys (figure 2b). These findings highlight several important facets of organismal and environmental interactions. These data support the observations that measures of reinforcing strength provide different information related to cocaine self-administration than measures of reinforcing effects. In addition, these findings indicate that after years of living in these stable groups the influence of the social context was still apparent.

A question that is frequently asked is ‘what if circumstances change and a dominant monkey becomes subordinate and a subordinate monkey becomes dominant?’ To address this question, we rearranged groups such that one pen consisted of four previously dominant (first-ranked) monkeys and another pen was made up of four previously subordinate (fourth-ranked) monkeys. Additional pens were composed of intermediate (second- and third-ranked) monkeys and experimentally naive monkeys (Czoty *et al.* in preparation). After three months of social housing under these new conditions, PET studies were conducted and cocaine self-administration was examined under the concurrent schedule of reinforcement with food as the alternative. The relationship between new social rank and D₂ receptor

availability was not evident—that is, the newly dominant monkeys did not have significantly higher levels of D₂ receptor availability compared with newly subordinate monkeys. (Note, some of the dominant monkeys were previously subordinate and some of the subordinate monkeys were once dominant.) Also, there were no differences in cocaine choice between the monkeys. Additional studies using other measures, including novel object reactivity, noted that previous rank was more predictive of outcome than current rank. There is a long and extensive literature on behavioural and pharmacological history influencing behaviour and drug effects (e.g. Barrett *et al.* 1989) and these studies extend those findings to include a history of social interactions.

Another example of organism $\times$ environment interaction involves the use of socially housed monkeys to examine drug-induced changes in social behaviour and the consequence of those effects on subsequent cocaine self-administration. There is an extensive literature on the interaction of social rank with drug effects in non-human primates (e.g. Smith & Byrd 1985; Martin *et al.* 1990; reviewed by Miczek *et al.* 2004). For example, Miczek and colleagues (e.g. Miczek & Yoshimura 1982; Miczek & Gold 1983a) have shown that the effects of alcohol, amphetamine or cocaine can be influenced by social rank and environmental context. In one study (Winslow & Miczek 1985), low to intermediate doses of alcohol produced increases in aggression by dominant monkeys, but no effect on aggression by subordinate animals. However, co-administration of alcohol and testosterone to subordinate monkeys resulted in increases in aggression. Crowley *et al.* (1974, 1992) examined the effects of a number of abused drugs on the social behaviour of macaques. Methamphetamine produced pronounced increases in locomotion and stereotypes, and declines in food-foraging behaviour and aggression. In a low-ranking monkey, high doses of methamphetamine produced such profound increases in submissive behaviours that the amount of aggression directed from the (untreated) dominant monkeys towards the drug-treated animal increased. Of all the studies examining the effects of drugs on social behaviour, this result is one of the few descriptions of the behaviour of the untreated monkeys. In our socially housed monkeys, we tested the hypothesis that if reinforcing doses of cocaine resulted in increased aggression and changes in social rank, then the frequency of cocaine self-administration in that monkey would increase in subsequent experimental sessions.

Monkeys lived in stable social groups of three and social rank was determined in each pen as described above. For these studies, only one monkey in the social group was given access to cocaine (saline, 0.01–0.1 mg kg⁻¹ injection⁻¹) under an FR 50 schedule of reinforcement, while the remaining monkeys in the pen had access to food presentation under an FR 50 schedule; conditions remained in effect for five consecutive sessions. When the session was completed, monkeys were returned to their social groups and agonistic and submissive behaviours were recorded over a 15 min period. All monkeys

(dominant, intermediate and subordinate) were studied at all cocaine doses. Social interactions did not affect response rates or cocaine intake for any monkey. However, cocaine-induced changes in social behaviour were dependent on the rank of the monkey. Irrespective of which animal in the pen self-administered cocaine, the first- and second-ranked monkeys showed increases in aggression; the subordinate monkey never demonstrated any aggression during the course of the study. These data indicate that social rank is the most important determinant of cocaine-induced changes in social behaviour. One possible reason that self-administration was insensitive to the consequences of social behaviour is that cocaine access was not scheduled until approximately 24 hours after the social interaction. Current studies are examining the consequences of cocaine-induced changes in social behaviour on cocaine self-administration that are more closely associated in time.

2. CONCLUSIONS

The goal of this review was to highlight several important factors that mediate drug abuse using animal models. All animal models are, as a minimum, predictive of some clinical outcome. Animal models of drug self-administration are perhaps the most reliable animal model of a human condition available to researchers (see Griffiths *et al.* 1980). When social behaviour of non-human primates and cocaine self-administration are included, these models are homologous models of human drug abuse. We described studies that investigated behavioural and neuropharmacological variables that have been identified as trait variables to a vulnerable phenotype. We also described situations in which social and environmental conditions produced changes that increased or decreased vulnerability to drug abuse.

When considering models of drug addiction, researchers have focused on factors that can increase or decrease drug self-administration. For example, we have known for some time that stress can increase vulnerability to self-administer cocaine. Perhaps more clinically significant is the understanding that environmental enrichment can attenuate the reinforcing effects of drugs. Not only has it been shown that alternative non-drug reinforcers can decrease vulnerability (Carroll *et al.* 1989) and maintenance of cocaine self-administration (Nader & Woolverton 1991, 1992), but that experience with these alternative reinforcers, frequently referred to as environmental enrichment, can profoundly decrease cocaine reinforcement. As a final example for this review, we highlight two preliminary studies that have documented these divergent effects on cocaine reinforcement in socially housed monkeys. Acute stressors, such as being an intruder into a pen of other monkeys (see Miczek & Gold 1983b; Miczek & Tidey 1989) can affect the reinforcing strength of cocaine. Although data are preliminary, it appears that the effects of being an intruder in an established social group are different depending on the social rank of the intruder. When a subordinate monkey is an intruder to a well-established pen of four socially housed male monkeys, the

subordinate animal's cocaine dose-response curve is likely to shift to the left, while the same intruder manipulation with a dominant monkey can result in rightward shifts in the cocaine dose-response curve. On the other end of the continuum, placing monkeys (irrespective of social rank) into larger enclosures with novel objects for 3 days prior to studying self-administration resulted in shifts to the right in the cocaine dose-response curve, such that doses that were chosen over food prior to the enrichment condition were no longer reinforcing. These findings suggest that environmental enrichment, even to monkeys that have been exposed to chronic stressors, such as subordinate animals, can produce powerful effects on the likelihood of drug self-administration. These findings are consistent with human studies showing that alternative reinforcers and environmental enrichment can increase the duration of abstinence from cocaine (Higgins 1997). The research described in this review has consistently shown that the environment can have profound effects on drug use and that there are neurobiological changes that accompany these effects. We believe the combination of environmental enrichment and pharmacotherapy will be most effective in treating cocaine addiction.

All experimental manipulations described in this review were performed in accordance with the National Research Council *Guidelines for the Care and Use of Mammals in Neuroscience and Behavioral Research* and were approved by the Animal Care and Use Committee of Wake Forest University. Environmental enrichment was provided as outlined in the Animal Care and Use Committee of Wake Forest University Non-Human Primate Environmental Enrichment Plan.

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