Available online at www.sciencedirect.com
SCIENCE DIRECT®
Neuroscience and Biobehavioral Reviews 27 (2004) 813–820
NEUROSCIENCE AND BIOBEHAVIORAL REVIEWS
www.elsevier.com/locate/neubiorev

Review

The expanding effects of cocaine: studies in a nonhuman primate model of cocaine self-administration

Linda J. Porrino*, James B. Daunais, Hilary R. Smith, Michael A. Nader

Department of Physiology and Pharmacology, Center for the Neurobiological Investigation of Drug Abuse, Wake Forest University School of Medicine, Winston Salem, NC 27157, USA

Abstract

Although neuroimaging investigations in human cocaine abusers have provided important insights into the brain changes that accompany drug use, the interpretation of reports in human abusers can be very difficult. Studies in nonhuman primates provide a way to systematically evaluate the structural and functional adaptations engendered by cocaine self-administration without the confounds of human research. Functional activity, measured with metabolic mapping methods, and markers of the dopamine system, assessed autoradiographically, were evaluated over the course of chronic cocaine self-administration (5 days, 3.3 months, and 15–22 months). Within the striatum the topography of these responses shifts dramatically over time. Changes in functional activity and alterations in the dopamine system occupy larger and larger portions of dorsal and ventral striatum with increasing durations of cocaine exposure. The growing impact of cocaine suggests that the elements of the behavioral repertoire outside of the influence of cocaine become smaller and smaller with increasing durations of exposure to drug use resulting in cocaine's dominance over all aspects of the addict's life.

Keywords: Cocaine; Striatum; Dopamine; Cerebral metabolism; Monkey

Contents

Although the acute effects of cocaine are relatively brief, persistent alterations in neural function that far outlast the presence of cocaine at its binding sites are also engendered. A vast body of research has focused on the question of potential structural and functional adaptations that occur along the course of cocaine use and abuse. The clinical course of cocaine abuse has been characterized as progressing through a number of temporal stages that advance from initial experimentation through casual use and finally to addiction. A number of investigators have described the longitudinal course of cocaine abuse in terms of clearly definable clinical phases [1–4]. Reports by cocaine users portray their initial experience with cocaine as highly pleasurable. Cocaine induces intense feelings of euphoria and well-being, along with an intensification of emotions and sexual feelings [3,5]. In those individuals who continue to use the drug, use patterns shift from casual occasional use to high-dose, long duration binges, sometimes accompanied by intense feelings of craving and a decreased sensitivity to the negative effects of the drug [3,4]. With continued high-intensity use and binging, reports of panic attacks, paranoia, and intense anxiety are frequent [1].

Underlying the temporal course of cocaine addiction and abstinence from cocaine are changes within the central nervous system as brain systems adapt to, and compensate for, cocaine use and the cessation of its use. Some of the most provocative data describing these changes have come from studies in human cocaine users. Investigations with

* Corresponding author. Address: Department of Physiology and Pharmacology, Wake Forest University School of Medicine, Medical Center Boulevard, Winston Salem, NC 27157-1083, USA. Tel.: +1-336-716-8575; fax: +1-336-716-8501.
E-mail address: lporrino@wfubmc.edu (L.J. Porrino).

0149-7634/$ - see front matter © 2003 Elsevier Ltd. All rights reserved.
doi:10.1016/j.neubiorev.2003.11.013

positron emission tomography (PET) as well as studies of post-mortem tissue have provided important insights into the nature of these processes [6,7].

Although studies in human addicts can address these issues directly, the interpretation of studies in humans can be limited by a large number of factors. One of the most problematic of these issues is the contemporaneous use of multiple drugs, both legal and illegal. Exposure to high levels of alcohol, caffeine and nicotine is a consistent characteristic of almost all chronic drug users. The interaction of these and other illegal drugs such as ecstasy, heroin and marijuana with cocaine, in combination with the structural and functional effects that chronic use of these drugs may produce render it exceedingly difficult to attribute any adaptations, whether they are behavioral or neurobiological, directly to cocaine itself.

Another problematic issue is the history of drug experience. Abusers report considerably different patterns of use, durations of exposure, quality or purity of cocaine, routes of administration, periods of abstinence, and total lifetime intake. Although self-report can be reliable in some instances, overall the accuracy of even recent drug use is often highly suspect in this population. This is further complicated by the difficulties faced in studies in which post-mortem tissue is utilized. Moreover, human drug abusers often have signs of other forms of psychopathology. Most prominently, depression and attention deficit disorder are the most common co-morbid diagnoses. Obtaining detailed histories of these conditions can be challenging, making it difficult to determine whether these conditions pre-date cocaine use or are the result of chronic drug exposure, but again co-morbid psychiatric conditions can further complicate the interpretation of human studies.

Finally, the majority of studies investigating the neurobiological basis of the effects of cocaine in humans have been carried out with cocaine-dependent subjects, at times in active treatment programs. Because substantial structural and functional changes accompany chronic cocaine use [8–10], the functional responses of chronic drug abusers used in most human studies are likely to be quite different from those of subjects with minimal drug exposure. Few studies, however, have been carried out in human subjects with little or no drug experience. Therefore, it is not possible to evaluate the temporal course of the neuroadaptations that accompany drug use, particularly without assessments of the functional response to cocaine in the earliest stages of drug exposure. Thus, the very nature of human research precludes a systematic evaluation of many of the variables that may result in neuroadaptations to the effects of drug exposure.

1. Advantages of nonhuman primate models of drug use

An alternate approach is the use of animal models in which carefully controlled experiments can be conducted. Nonhuman primates have been used in intravenous self-administration studies for nearly 40 years and have proved a valid and reliable model of human drug abuse [5,11,12]. Thus, there is a large database of scientific information upon which to draw for interpretation of results. In addition to this, there are several advantages to using nonhuman primates in research compared to other animal models. Monkeys have greater than 95% gene homology with humans [13]. As a result, nonhuman primates are more similar to humans in phylogeny, anatomy, physiology and behavior, enhancing our ability to accurately generalize our findings to human drug abuse. For example, abundant evidence indicates that there are differences between rodents and primates in the anatomy, physiology and neurochemistry of brain DA systems [14–17]. Furthermore, nonhuman primate brain differs substantially from the rodent brain in terms of cocaine-induced changes in brain metabolism [18,19] and on dopamine transporter levels [20]. Finally, the neuroendocrine system of nonhuman primates, particularly the HPA axis, is very similar to humans and therefore the interactions of drug effects with stress provide an appropriate model of the human condition [21].

In the first publication utilizing the drug self-administration model [22], monkeys were studied 24 h per day under conditions in which drug self-administration was examined along with other nondrug reinforced behaviors. A hallmark of this first publication and a unique characteristic of nonhuman primate research is the characterization of individual-subject behavior. As it pertains to models of drug abuse, this allows for the study of individual differences, which is an important characteristic of human drug addiction. When self-administration is combined with various imaging modalities (briefly discussed below), the ability to correlate drug- and nondrug-maintained behavior to various CNS markers allows for the development of extremely powerful animal models of ‘vulnerability’, ‘maintenance’ and ‘relapse’. A final point to be made regarding the behavior is that nonhuman primates can learn complex tasks that are more applicable to human drug seeking compared to other animal species.

In addition to genetic homology and stability and complexity of behavior, nonhuman primates are also advantageous as research subjects because of their long life span, which can exceed 30 years in captivity. Thus, long-term, within-subjects, longitudinal studies can be incorporated to characterize the progression of changes across time. The subject serving as its own control is highly advantageous, as is the ability to start with drug-naïve subjects, allowing for the study of neuronal adaptation to drug exposure. Nonhuman primate models are ideally suited for this type of investigation.

Nonhuman primates can be used in several protocols to examine neuronal adaptations. Much of the research reviewed here involved the study of differences in receptor

densities in monkeys with certain cocaine self-administration histories compared to food-reinforced control monkeys. These studies provide unequivocal evidence for changes in dopamine receptor densities due to reinforcing doses of cocaine. The size of the nonhuman primate brain allows for examination of several receptor systems, as well as tissue for other neuronal markers using in situ hybridization, microarrays or other methodologies. The ability to study multiple systems at the same time point in the progression of drug exposure is extremely advantageous to understanding the sequelae of events leading to neuronal adaptation.

2. Focus on the striatum

One of the goals of the work briefly reviewed here was a systematic evaluation of the development or progression of changes in the structural and functional response to cocaine spanning from initial experimentation to casual or recreational use to more chronic exposure and eventually addiction. Although the temporal course of the neuroadaptations that result from chronic cocaine is apparent in many regions of the brain, this progression is most evident in the striatum.

The striatum is often considered in terms of functional domains based on inputs it receives from the cortical mantle (Fig. 1). The sensorimotor striatum includes most of the caudate and putamen caudal to the decussation of the anterior commissure and the most dorsolateral portions of the caudate and putamen rostral to it. The association striatum includes most of the caudate and the central putamen rostral to the anterior commissure. Finally, the limbic striatum comprises the nucleus accumbens, shell and core, and the surrounding ventral putamen and ventral caudate. For more detailed descriptions see Refs. [23,24]. Each striatal region is influenced to a differing degree by topographically organized inputs from the cortex, ventral midbrain, and limbic structures [25–27], thereby defining its functionality as sensorimotor, association-cognitive, or limbic-motivational. In the studies described here, this heterogeneity of striatal function has been taken into account by analyzing the entire dorsoventral, mediolateral, rostrocaudal extent of the striatum, considering each domain in the course of this analysis.

3. Initial phases of cocaine exposure

In order to assess the neurobiological response to cocaine throughout the entire brain and in particular across the full extent of the striatum in nonhuman primates, metabolic mapping with the 2-[^{14}C]deoxyglucose method was used. In a series of studies this approach, along with other imaging methods, has been used to visualize the effects of cocaine in nonhuman primates under a variety of experimental conditions in which dose and duration of cocaine exposure were systematically varied (Fig. 2). In our first studies [18,28], we examined the effects of an acute infusion of cocaine (1.0 mg/kg) in a group of cocaine-naïve monkeys. Although the functional consequences of cocaine administration encompassed the basal ganglia, prefrontal cortex, thalamus, and hippocampus, within the striatum the most intense effects were localized in the ventral portions of the striatum including the nucleus accumbens and the olfactory tubercle. However, there were also widespread effects in the dorsal striatum throughout both the caudate and putamen. This suggests that an initial experience with the subjective sensations produced by cocaine in nonhuman primates is relatively nonspecific within the striatum with effects on sensorimotor and cognitive functions, as well effects in reward systems.

In a second series of studies, still during the initial phases of drug exposure, the effects of cocaine were evaluated following self-administration (Fig. 2) [19]. For these studies, all monkeys performed an operant task to receive

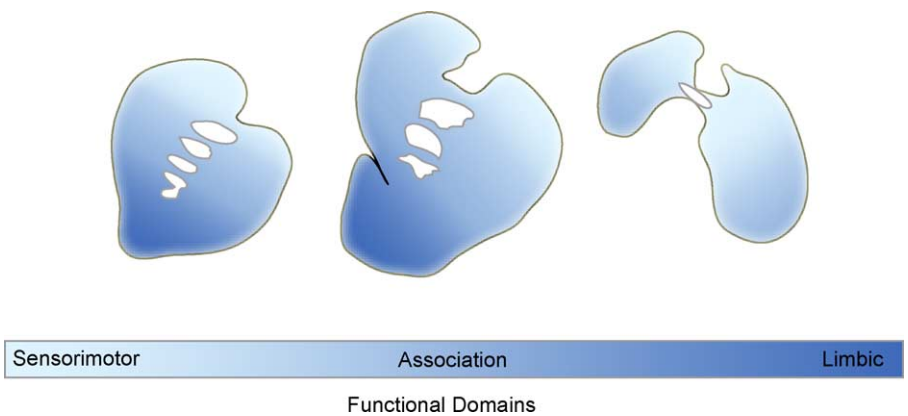

Fig. 1. Functional domains within the striatum are based on overlapping cortical inputs. The limbic domain is the ventral striatum (dark blue) and receives inputs from orbital and limbic cortex. The association domain is the central striatum (medium blue) and receives inputs from dorsolateral prefrontal, temporal and parietal association cortex. The sensorimotor domain is the dorsolateral striatum (light blue) and receives inputs from motor and sensory cortex. AC, anterior commissure.

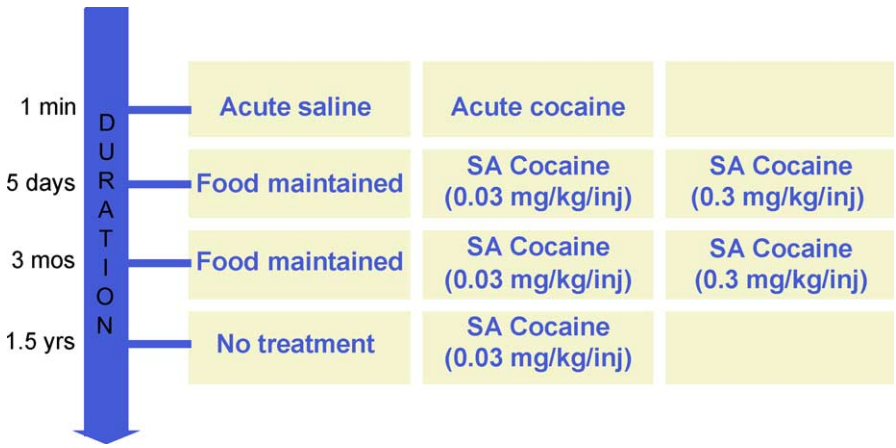

Fig. 2. Experimental summary. Shown are the groups of animals evaluated in the studies described here, organized according to the duration of cocaine exposure and the dose of cocaine administered. SA, self-administration.

food or cocaine. Responding by the monkeys was maintained under a fixed-interval (FI) 3-min schedule, with monkeys self-administering cocaine (0.03 or 0.3 mg/kg/inj) over five sessions for a total of 4.5 or 45 mg/kg total intake. Mapping took place at the end of the fifth cocaine self-administration session at a time chosen to insure that cocaine was clearly acting as a reinforcer, but before its use was likely to result in significant neuroadaptations. Cocaine self-administration resulted in significant dose-dependent changes in glucose utilization throughout all levels of the ventral striatum, as well as in the caudate rostral to the anterior commissure (Fig. 3). There were, however, no changes in the putamen at any level. If we consider the functional domains of the striatum, then at this early stage of cocaine self-administration, cocaine's influences were restricted to the limbic domain subserving emotional and motivational functions, with smaller influences in cognitive domains, but little effect in sensorimotor striatal regions.

In the initial stages of exposure to cocaine, as expected there were few effects on the regulation of dopamine receptors. No significant changes in the density of either dopamine D_1 or D_2 binding sites (Fig. 4) were identified [29]. There was, however, some evidence for an alteration in the regulation of dopamine transporters [20]. Decreases in the concentration of dopamine transporter binding sites was evident in the ventral striatum just rostral to the anterior commissure, the same area of the ventral striatum in which the greatest changes in functional activity were produced by cocaine at this time.

Overall, the topography of the distribution of alterations in functional activity and dopamine systems appears to reflect the degree of increase in the concentration of extracellular dopamine. Recent studies [30,31] have shown that cocaine self-administration produces the greatest elevations in dopamine levels in the ventral striatum with the magnitude of increase diminishing in more dorsal striatum. Although structural adaptations at this time point were minimal, the area within the striatum most vulnerable to such changes was the limbic domain. Cocaine in the earliest stages of exposure, as modeled here in these studies by short-term cocaine self-administration in nonhuman primates, therefore, impacts largely the portions of

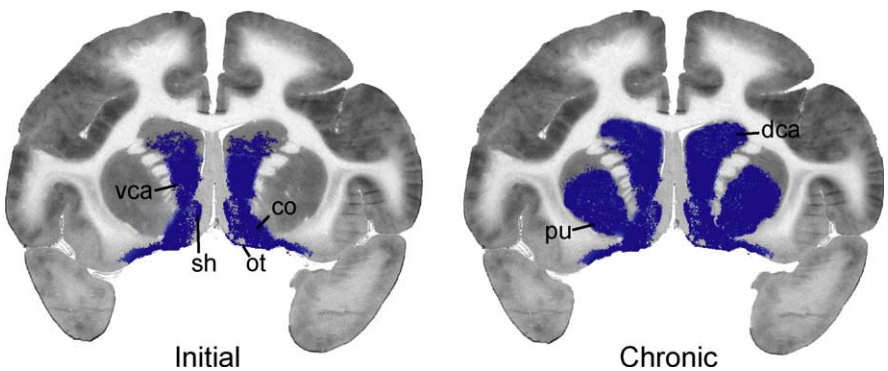

Fig. 3. Areas of cerebral metabolic response produced by self-administered cocaine in the striatum of rhesus monkey. Shown are representative autoradiograms of 2-[^{14}C]deoxyglucose uptake in coronal sections at a caudal level of the pre-commissural striatum, +2.5 from bregma (Paxinos et al., 2000). Areas shown in blue depict those areas in which significant decreases in rates of glucose utilization were measured in the initial (left) and chronic (right) stages of cocaine self-administration experience. Abbreviations are: sh, nucleus accumbens-shell; co, nucleus accumbens-core; ot, olfactory tubercle; dca, dorsal caudate; vca, ventral caudate; pu, putamen.

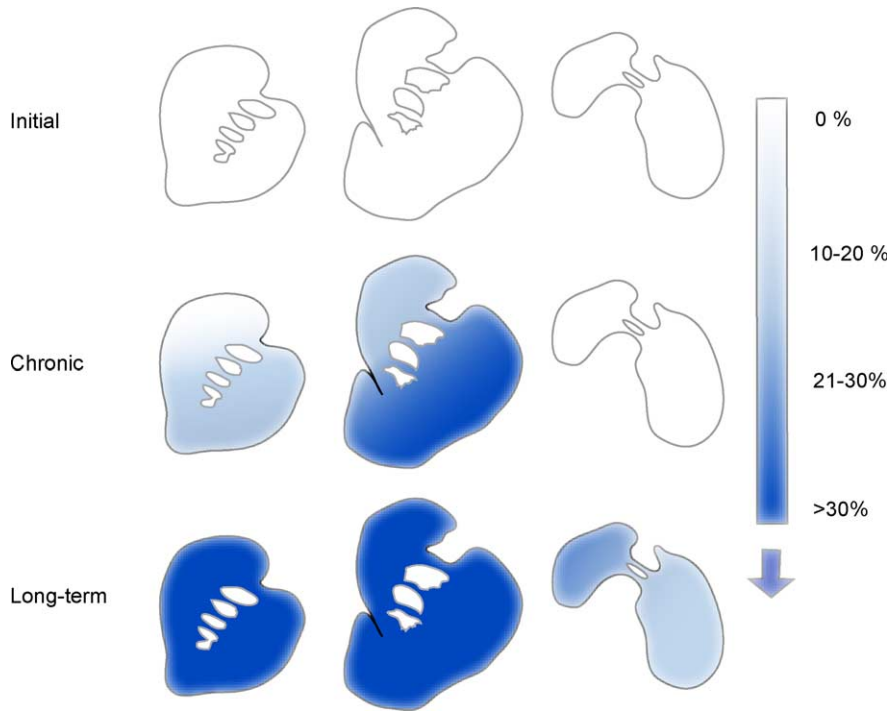

Fig. 4. Time course of effects on D_2 receptor density. Schematic diagrams illustrating changes in the density of D_2 receptor binding sites in rostral (left) and caudal (center) pre-commissural and post-commissural (right) striatum of monkeys in the initial (5 days), chronic (3.3 months), and long-term (1.5 years) stages of self-administration. Colors represent ranges of % changes in binding densities as compared to control values: white, $<10\%$ change; light blue, 10–20% decrease; medium blue, 21–30% decrease; dark blue, $>30\%$ decrease.

the striatum that are involved in the processing of reward and motivational information with smaller or no effects on other functional domains.

4. Chronic phases of cocaine exposure

A second series of studies examined the effects of repeated exposure to cocaine, evaluating changes in the functional response to cocaine after 3.3 months of daily cocaine self-administration, as well as the adaptations in dopamine systems that resulted from the chronic exposure [20,28,29]. Here, monkeys self-administered either 0.03 or 0.3 mg/kg/inj and had self-administered approximately 90 or 900 mg/kg, respectively, by the end of the 3.3 months. This time point was chosen in an attempt to model the effects of repeated use of cocaine beyond the stage of casual or merely recreational drug use.

Following these longer durations of self-administration experience, the pattern of functional changes in the ventral striatum, as assessed by the 2-[^{14}C]deoxyglucose method, resembled the metabolic alterations in the initial stages of cocaine exposure, except they were more intense. Within the dorsal striatum, however, when compared to those in the initial stages, the functional effects of cocaine self-administration broadened to encompass a wider expanse of the caudate and putamen. The striatal territory affected by cocaine spread rostrally and dorsally to include almost the entire extent of the dorsal striatum rostral to the anterior commissure (Fig. 2). In addition, there was evidence for changes in cerebral metabolism in portions of the caudate and putamen caudal to the anterior commissure as well. This topography of the response to repeated cocaine exposure suggests that with increased experience cocaine's influence spreads over the processing of sensorimotor, cognitive as well as motivational information.

An important consideration is the circuitry that underlies the gradual expansion of the functional response to cocaine. Haber and colleagues [32] have recently described the complex organization of striato-nigro-striatal circuitry and how this circuitry provides a means through which information flow between striatal regions can be achieved. They have shown that each striatal region is connected reciprocally with the ventral midbrain. This circuitry can be characterized as a series of ascending spiraling connections between adjacent striatal regions via the ventral midbrain. In effect, the shell influences the core, the core influences the central striatum, and the central striatum influences the dorsolateral striatum in turn. This hierarchical arrangement provides an anatomical framework for the expanded functional changes in the striatum that accompany cocaine self-administration and support for the notion that the pattern of afferents to the striatum determines the functional response to cocaine.

Chronic exposure to cocaine self-administration also led to significant changes in the regulation of dopamine systems within the striatum. One of the most prominent effects

was the appreciable down-regulation of D_2 receptors [29]. The topography of these alterations in binding patterns paralleled the functional changes observed with metabolic mapping methods. Specifically, the largest decrements in the concentration of the D_2 receptor sites were found in the ventral striatum, core and shell of the nucleus accumbens. Within the dorsal striatum, decreased densities of receptors were seen in most portions of the caudate rostral to the anterior commissure, but not in any portion of the caudate or putamen caudal to it (Fig. 4).

Following even more prolonged periods (15–22 months) of self-administration of cocaine [33] greater down-regulation of D_2 receptors was evident (Fig. 4). Decreased receptor density was present in all of the rostral pre-commissural striatum and large portions of the post-commissural striatum as well. So with longer exposure to cocaine, the decreases in D_2 receptor density grew more intense and incorporated more dorsal and rostral regions of the striatum, as well as now the changes extended into the post-commissural sensorimotor striatum.

These data clearly show then, that the changes in D_2 receptor numbers are a result of cocaine exposure, not just a pre-existing condition. Moreover, it is interesting to note that the changes in the dopamine system appear to lag behind the functional changes with areas showing alterations in the concentrations of dopamine receptors and transporters after these areas are affected functionally. The functional changes then are predictive of the appearance of structural changes after longer periods of exposure to cocaine.

Another interesting conclusion from these studies is that the dose of cocaine appeared less important than the duration of exposure. After 3.3 months of self-administration experience with total intakes of approximately 90 and 900 mg/kg for the low and high-dose groups, respectively, similar changes occurred in the distribution of D_2 receptors regardless of the dose of cocaine. The conclusion is further supported by the fact that at 15–22 months drug exposure, total intake was less than the high-dose group at 3.3 months, yet the receptor changes were far more extensive with a longer duration of drug exposure [29,33]. This suggests that environmental modulation, in terms of stimuli associated with cocaine-seeking, may be as important to dopamine receptor changes as direct pharmacological consequences of cocaine exposure. The entire behavioral repertoire, then, not just the pharmacology of cocaine, significantly impacted D_2 receptor numbers.

In contrast, the density of dopamine transporter binding sites was shown to change as a factor of both time and dose [20]. In contrast to the decreases observed after 5 days of cocaine self-administration, 3.3 months of drug exposure resulted in large *increases* in dopamine transporter binding site levels (Fig. 5) at this level of the striatum. Elevations in dopamine transporter binding sites were most evident in the ventral striatum. At the higher dose, the effects on dopamine transporter binding were greater and encompassed more of the rostral-most part of the striatum. As was the case with D_2 receptors, no alterations in the concentration of dopamine transporter binding sites was evident caudal to the anterior commissure. However, in

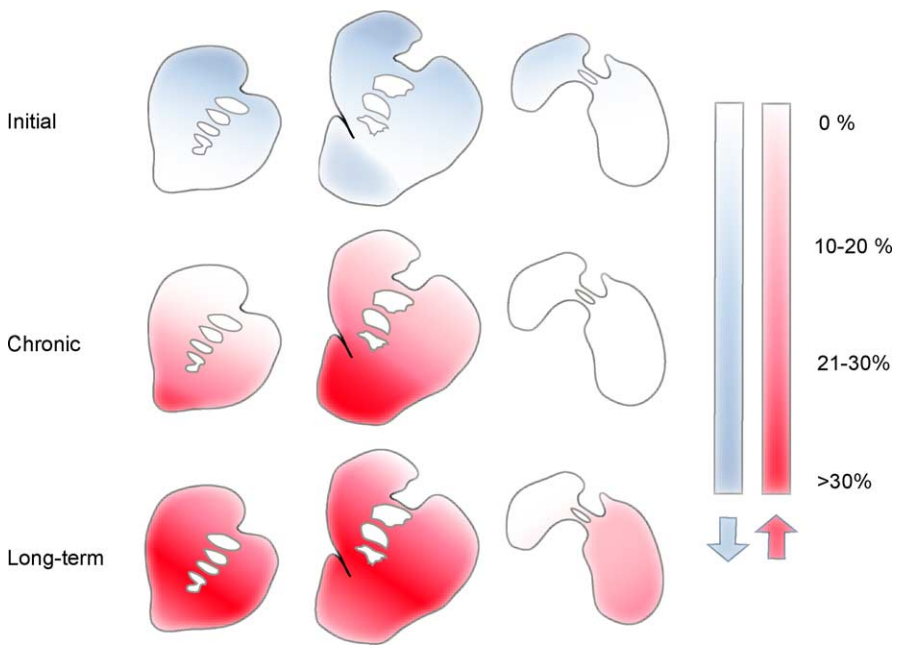

Fig. 5. Time course of effects on DAT density. Schematic diagrams illustrating changes in the density of DAT binding sites at rostral (left) and caudal (center) pre-commissural and post-commissural (right) striatum of monkeys in the initial (5 days), chronic (3.3 months), and long-term (1.5 years) stages of self-administration. Colors represent ranges of % changes in binding densities as compared to control values: light blue, 10–20% decrease; medium blue, 21–35% decrease; white, $<10\%$ change; light red, 10–20% increase; medium red, 21–35% increase; dark red, $>35\%$ increase.

a group of monkeys that self-administered cocaine for 15–22 months, alterations in dopamine transporter (Fig. 5) also appeared to spread rostrally and dorsally, involving both limbic and association domains, but also affected dopamine transporters throughout sensorimotor processing regions of the striatum, especially in those striatal areas caudal to the anterior commissure. In summary, with higher doses and longer exposure to cocaine, the increases in the density of the dopamine transporter grew more intense and incorporated larger expanses of striatal territory, thereby having an influence on the processing of neuronal signaling underlying a wide range of behavioral phenomena.

5. Conclusions

The overall goal of the studies reviewed here was to evaluate the structural and functional adaptations engendered by cocaine exposure in a nonhuman primate model of substance abuse. We have examined the temporal progression of these adaptations as self-administration advances from its initial stages (5 days) through a chronic phase (3.3 months) to a prolonged phase (15–22 months) of drug exposure. These time points were chosen to reflect the transition from casual use of cocaine to more repeated use and on to the compulsive use that is a hallmark characteristic of addiction. Each stage in the development of addiction is accompanied by neurobiological adaptations to drug exposure. Although cocaine administration in nonhuman primates is only a model of drug use in humans and may not represent all of the elements of human cocaine-seeking, the assessment of the earliest stages of drug use has provided a picture of the initial stages of drug exposure, not possible in human subjects. Furthermore, we have been able to follow the shifts in the neural response to cocaine along the temporal course of this transition to addiction.

Throughout this course cocaine influences functional activity in a highly discrete network of inter-connected limbic brain regions, but its primary effects are in the striatum. The anatomical topography of the functional response within the striatum, however, shifts dramatically. Changes in functional activity and alterations in the regulation of the dopamine system occupy larger and larger portions of the striatum with increasing durations of cocaine exposure. This progression is in fact quite orderly and follows defined anatomical principles of organization within the striatum and its extrinsic connections with cortex and the dopaminergic ventral midbrain [32].

Recent conceptions of addiction have focused on the habitual or compulsive nature of drug use in addicts with the idea that control over drug use evolves from action to habit [34–37] by shifting from goal-directed processes to habit-based control. This shift suggests a change in the neuroanatomical substrates of the behavior patterns, moving from ventral striatum underlying goal-directed learning processes [38] to the dorsal striatum necessary for habit formation [39]. The progressive increase in the response to cocaine advancing from the ventromedial motivational limbic domains of the striatum through cognitive-association domains to sensorimotor regions observed in the studies reviewed here provides an anatomical basis for this behavioral shift. The growing impact of cocaine further suggests that the elements of the behavioral repertoire outside of the influence of cocaine become smaller and smaller with increasing durations of exposure to drug use resulting in cocaine's dominance over all aspects of the addict's life.

Acknowledgements

The authors dedicate this work to our friend Roger Brown without whom none of this would have been possible. This work was supported by National Institutes of Health grants from the National Institute on Drug Abuse DA09085, DA10230 and DA06634.

References

[1] Post RM, Weiss SR. Psychomotor stimulant vs. local anesthetic effects of cocaine: role of behavioral sensitization and kindling. NIDA Res Monogr 1988;88:217–38.
[2] Gawin FH, Kleber HD. Abstinence symptomatology and psychiatric diagnosis in cocaine abusers. Clinical observations. Arch Gen Psychiatry 1986;43:107–13.
[3] Gawin FH. Cocaine addiction: psychology and neurophysiology. Science 1991;251:1580–6.
[4] Gawin FH. Cocaine addiction: psychology, neurophysiology and treatment. In: Korenam SG, Barchas JD, editors. Biological basis of substance abuse. New York: Oxford University Press; 1993. p. 425–42.
[5] Johanson CE, Fischman MW. The pharmacology of cocaine related to its abuse. Pharmacol Rev 1989;41:3–52.
[6] Volkow ND, Fowler JS. Addiction, a disease of compulsion and drive: Involvement of the orbitofrontal cortex. Cereb Cortex 2000;10: 318–25.
[7] Porrino LJ, Lyons D, Letchworth SR, Freedland CS, Nader MA. Structural and functional neuroimaging of the effects of cocaine on human and non-human primates. In: Massaro EJ, editor. Handbook of neurotoxicology. Totowa, NJ: Humana Press; 2000. p. 413–35.
[8] Volkow ND, Wang GJ, Fowler JS, Hitzemann R, Angrist B, Gatley SJ, Logan J, Ding YS, Pappas N. Association of methylphenidate-induced craving with changes in right striato-orbitofrontal metabolism in cocaine abusers: implications in addiction. Am J Psychiatry 1999; 156:19–26.
[9] Strickland TL, Miller BL, Kowell A, Stein R. Neurobiology of cocaine-induced organic brain impairment: contributions from functional neuroimaging. Neuropsychol Rev 1998;8:1–9.
[10] Kaufman MJ, Levin JM, Maas LC, Kukes TJ, Villafuerte RA, Dostal K, Lukas SE, Mendelson JH, Cohen BM, Renshaw PF. Cocaine-induced cerebral vasoconstriction differs as a function of sex and menstrual cycle phase. Biol Psychiatry 2001;49:774–81.
[11] Mello NK, Negus SS. Preclinical evaluation of pharmacotherapies for treatment of cocaine and opioid abuse using drug self-administration procedures. Neuropsychopharmacology 1996;14:375–424.

[12] Griffiths RR, Bigelow GE, Henningfield JE. Similarities in animals and human drug-taking behavior. In: Mello NK, editor. Advances in substance abuse. Greenwich, CT: JAI Press; 1980. p. 1–90.
[13] Hacia JG, Makalowski W, Edgemon K, Erdos MR, Robbins CM, Fodor SP, Brody LC, Collins FS. Evolutionary sequence comparisons using high-density oligonucleotide arrays. Nat Genet 1998;18:155–8.
[14] Haber SN, McFarland NR. The concept of the ventral striatum in nonhuman primates. Ann N Y Acad Sci 1999;877:33–48.
[15] Berger B, Gaspar P, Verney C. Dopaminergic innervation of the cerebral cortex: unexpected differences between rodents and primates. Trends Neurosci 1991;14:21–7.
[16] Joel D, Weiner I. The connections of the dopaminergic system with the striatum in rats and primates: an analysis with respect to the functional and compartmental organization of the striatum. Neuroscience 2000;96:451–74.
[17] Cragg SJ, Hille CJ, Greenfield SA. Dopamine release and uptake dynamics within nonhuman primate striatum in vitro. J Neurosci 2000;20:8209–17.
[18] Lyons D, Friedman DP, Nader MA, Porrino LJ. Cocaine alters cerebral metabolism within the ventral striatum and limbic cortex of monkeys. J Neurosci 1996;16:1230–8.
[19] Porrino LJ, Lyons D, Miller MD, Smith HR, Friedman DP, Daunais JB, Nader MA. Metabolic mapping of the effects of cocaine during the initial phases of self-administration in the nonhuman primate. J Neurosci 2002;22:7687–94.
[20] Letchworth SR, Nader MA, Smith HR, Friedman DP, Porrino LJ. Progression of changes in dopamine transporter binding site density as a result of cocaine self-administration in rhesus monkeys. J Neurosci 2001;21:2799–807.
[21] Morgan D, Grant KA, Gage HD, Mach RH, Kaplan JR, Prioleau O, Nader SH, Buchheimer N, Ehrenkaufer RL, Nader MA. Social dominance in monkeys: dopamine D2 receptors and cocaine self-administration. Nat Neurosci 2002;5:169–74.
[22] Thompson T, Schuster CR. Morphine self-administration, food reinforcement, and avoidance behaviors in rhesus monkeys. Psychopharmacologia 1964;5:87–94.
[23] Haber SN, Fudge JL. The primate substantia nigra and vta: integrative circuitry and function. Crit Rev Neurobiol 1997;11:323–42.
[24] Lynd-Balta E, Haber SN. The organization of midbrain projections to the ventral striatum in the primate. Neuroscience 1994;59:609–23.
[25] Alexander GE, Crutcher MD. Functional architecture of basal ganglia circuits: neural substrates of parallel processing. Trends Neurosci 1990;13:266–71.
[26] Goldman-Rakic PS, Selemon LD. Topography of corticostriatal projections in non-human primates and implications for functional parcellation of the neostriatum. In: Jones EG, Peters A, editors. Cerebral cortex. New York: Plenum Press; 1986. p. 447–66.
[27] Haber SN, Kunishio K, Mizobuchi M, Lynd-Balta E. The orbital and medial prefrontal circuit through the primate basal ganglia. J Neurosci 1995;15:4851–67.
[28] Porrino LJ, Lyons D. Orbital and medial prefrontal cortex and psychostimulant abuse: studies in animal models. Cereb Cortex 2000; 10:326–33.
[29] Nader MA, Daunais JB, Moore T, Nader SH, Moore RJ, Smith HR, Friedman DP, Porrino LJ. Effects of cocaine self-administration on striatal dopamine systems in rhesus monkeys: initial and chronic exposure. Neuropsychopharmacology 2002;27:35–46.
[30] Bradberry CW. Acute and chronic dopamine dynamics in a nonhuman primate model of recreational cocaine use. J Neurosci 2000;20: 7109–15.
[31] Bradberry CW, Barrett-Larimore RL, Jatlow P, Rubino SR. Impact of self-administered cocaine and cocaine cues on extracellular dopamine in mesolimbic and sensorimotor striatum in rhesus monkeys. J Neurosci 2000;20:3874–83.
[32] Haber SN, Fudge JL, McFarland NR. Striatonigrostriatal pathways in primates form an ascending spiral from the shell to the dorsolateral striatum. J Neurosci 2000;20:2369–82.
[33] Moore RJ, Vinsant SL, Nader MA, Porrino LJ, Friedman DP. Effect of cocaine self-administration on dopamine d2 receptors in rhesus monkeys. Synapse 1998;30:88–96.
[34] Everitt BJ, Wolf ME. Psychomotor stimulant addiction: a neural systems perspective. J Neurosci 2002;22:3312–20.
[35] Berke JD, Hyman SE. Addiction, dopamine, and the molecular mechanisms of memory. Neuron 2000;25:515–32.
[36] Everitt BJ, Dickinson A, Robbins TW. The neuropsychological basis of addictive behaviour. Brain Res Brain Res Rev 2001;36:129–38.
[37] Robbins TW, Everitt BJ. Drug addiction: bad habits add up. Nature 1999;398:567–70.
[38] Parkinson JA, Cardinal RN, Everitt BJ. Limbic cortical–ventral striatal systems underlying appetitive conditioning. Prog Brain Res 2000;126:263–85.
[39] Mishkin M, Malamut B, Bachevalier J. Memories and habits: two neural systems. In: McGaugh JL, Weinberger NM, editors. Neurobiology of human learning and memory. New York: Guildford; 1984. p. 65–87.