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Dopamine in the Nucleus Accumbens During Cocaine Self-Administration as Studied by In Vivo Microdialysis

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PETTIT, H. O. AND J. B. JUSTICE, JR. *Dopamine in the nucleus accumbens during cocaine self-administration as studied by in vivo microdialysis*. PHARMACOL BIOCHEM BEHAV **34**(4) 899–904, 1989.—The extracellular dopamine (DA) concentration in the nucleus accumbens was measured following intravenous cocaine administration. The DA concentration increased in a dose-dependent manner following a single intravenous infusion of cocaine. The concentration of DA was observed to increase and stabilize in a schedule-dependent manner when cocaine was repeatedly administered 15-, 5- and 2.5-minute intervals. When cocaine was administered in regular intervals to animals by an experimenter or when animals self-administered cocaine, DA concentrations stabilized substantially above the basal level. These data support research that suggests that reinforcing properties of cocaine are primarily mediated by DA release in the nucleus accumbens. The data and pharmacokinetic calculations indicate that the DA concentration increases for a short period following each infusion. It then falls to a level until the animal again self-administers the drug. Animals may regulate self-administration responding for cocaine in order to maintain DA levels above a certain level, yet titrate responding so that aversive effects are not produced.

Microdialysis Cocaine Nucleus accumbens Self-administration Reinforcement

ACQUIRING detailed understanding of the effects of abused drugs in the central nervous system is a critical factor in resolving the problem of drug abuse. Refinements of in vivo microdialysis procedures have made it possible to monitor changes in the extracellular concentration of neurotransmitters during drug self-administration. Monitoring ongoing extracellular neurochemistry during drug self-administration can advance our understanding of the neuronal events that occur following the administration of abused drugs.

One notable characteristic of intravenous drug self-administration is that responding for drug administration occurs over regular intervals of time. In limited access conditions, regular interresponse intervals occur during intravenous self-administration of cocaine (13, 21, 22, 24), amphetamines (36,38), methylphenidate (32,33), heroin (7, 12, 13), morphine (29), and ethanol (35). Uniform interresponse intervals occur during the self-administration of a wide variety of abused drugs, and also are observed as the phylogenetic scale is ascended from rat to human. Regular intervals are observed in drug self-administration by rats (13,21), monkeys (1,33), and by humans (14, 23, 28). One major consequence of regular interresponse intervals is that consistent amounts of drug intake are observed both within, and between self-administration trials. Under limited access conditions (i.e., 3–8 hr/day), a stable level of drug intake is observed over time (24, 36, 37).

Response rates for intravenous drug self-administration vary inversely with drug dose. When dose is increased, the number of infusions observed during a given time period decreases. Likewise, when the drug dose is decreased, animals compensate by increasing the number of infusions they receive (21,24). It has been hypothesized that animals compensate response rate for changes in drug dose in order to regulate a constant level of drug intake over time (37). Yokel and Pickens (37) report that across a wide range of doses, self-administration animals maintain constant plasma and body concentrations of d- and l-amphetamine over time. These results have led to the suggestion that responding for stimulant drug administration occurs when the drug concentration in the body falls below a minimum level (24,40). Yokel and Pickens (37) also suggest that a specific concentration of amphetamine in the brain is maintained by rats which self-administer amphetamine (1.4 and 3.8 mg/kg for d- and l-amphetamine, respectively). The present study extends the above finding by demonstrating that a specific concentration of dopamine in the nucleus accumbens is maintained during cocaine self-administration.

The reinforcing properties of psychomotor stimulants, such as amphetamine and cocaine, are primarily mediated by dopamine (DA) release in the nucleus accumbens (N ACC). Both amphetamine and cocaine serve to increase the extracellular concentration of DA; cocaine by blocking the reuptake of DA (6,25), and amphetamine by both an increase in DA release, and by an inhibition of monoamine oxidase (17). Administration of dopaminergic antagonists will attenuate the intravenous self-administration of amphetamine and cocaine (5, 7, 38, 39). Furthermore, specific 6-hydroxydopamine lesions of DA terminals in the N ACC attenuate psychomotor stimulant self-administration (15, 20, 26, 27).

A specific extracellular concentration of cocaine should in-

crease the extracellular concentration of DA in brain areas which contain dopaminergic terminals. As a result of cocaine administration, the extracellular concentration of DA would be expected to increase in the N ACC, caudate, and medial prefrontal cortex (for example). Cocaine and DA concentrations in striatal extracellular fluid have been found to be linearly related (11,18). Although many brain areas will be affected by cocaine administration, DA release in the N ACC has been most closely linked with the mediation of drug-induced reinforcement (15, 20, 26, 27).

The current study was designed to test the hypothesis that animals which self-administer cocaine, increase and maintain the extracellular concentration of DA in the N ACC above basal levels. In vivo microdialysis procedures were used to monitor the extracellular concentration of DA in the N ACC following the intravenous administration of cocaine.

METHOD

Initial experiments in anesthetized animals quantified DA concentrations in the N ACC with respect to 1) the effects of a single intravenous infusion of four doses of cocaine, 2) repeated cocaine infusions, and 3) the effects of manipulating the schedule of repeated cocaine infusions. The extracellular concentration of DA in the N ACC was then examined in behaving animals during ongoing cocaine self-administration. Lastly, pharmacokinetic calculations derived from single infusion data were used to demonstrate the pharmacodynamics of DA during the self-administration of cocaine.

Subjects

Male Wistar rats (250–350 g) served as subjects in each experiment. Animals were maintained under an ad lib food and water schedule (except for a four-day food deprivation period in self-administration animals). All animals were subject to surgical procedures (jugular catheter and microdialysis probe implantation) that differed depending on whether or not studies used anesthetized or behaving animals.

Apparatus

The HPLC system has been described elsewhere (2,30). However, in the present experiments, a 0.5 mm i.d. column, and a EG&G Princeton Applied Research detector (Model 400) were used.

Microdialysis probes were constructed from two pieces of fused silica tubing (25 μm i.d.; 150 μm o.d.; Polymicro Technologies). The two pieces of tubing were placed side by side, and the ends of the inlet and outlet tubes were separated by two mm. A five-mm piece of dialysis membrane (300 μm o.d.; 5000 mw cutoff; Enka Glanztoff AG, West Germany) was placed over the ends of the fused silica. Polyamide resin (Alltech) was used to seal both ends of the dialysis membrane. The resin was also used to coat the excess portion of membrane so that the active area of the microdialysis probe that was exposed to extracellular fluid was two mm in length. The other end of the inlet line was inserted into a 26 gauge removable Hamilton needle, and sealed in place with epoxy. The inlet line was attached to a 250 μl Hamilton syringe that was mounted upon a Harvard syringe pump (Model 2274). Artificial cerebrospinal fluid (CSF) was then perfused through the dialysis probe (2,18). For on-line analyses the end of the outlet line was directly connected to the HPLC injector valve through a five cm piece of stainless steel tubing. For off-line microdialysis in self-administration animals, the inlet line was spliced and attached to a dual channel fluid swivel (BAS, one channel for CSF inflow and the other for cocaine infusion). The outlet line (15 inches in length) passed just outside the animals cage so that samples could be collected in a 0.2 ml tube (Eppendorf) mounted on the swivel. Additional details have been previously published (2, 3, 30).

Procedures

Surgical procedures. All animals received a silastic catheter implant into the right external jugular vein. In experiments utilizing anesthetized animals, the catheter exited out of the neck incision area and was connected to a syringe filled with a cocaine solution. Microdialysis procedures were implemented once animals were placed in a stereotaxic instrument, and a microdialysis probe was lowered into the nucleus accumbens. Stereotaxic coordinates were AP +3.0, L ±1.7, DV −8.1 mm from skull; incisor bar = +5.0 mm (19,20). Behaving (e.g., self-administration) animals also received a jugular catheter implant; however, the catheter passed from the heart, ran subcutaneously around the animal's neck, and exited on the dorsal surface of the skull. The catheter end was then attached to a mount (#313-001; Plastic Products) that was cemented on the animals skull. Following catheter implantation, a stainless steel guide cannula (20 g) was lowered with a stereotaxic instrument so that the cannula end was directly above the dorsal surface of the nucleus accumbens (coordinates as above, however, DV = −6.1). Microdialysis probes were designed to protrude two mm from the tip of the guide cannula. Immediately following surgery, self-administration animals were injected with penicillin to prevent bacterial infection (60,000 units, IM). Stainless steel stylets were used to keep guide cannula patent during a three-day surgical recovery period, and during acquisition of cocaine self-administration. All animals were initially anesthetized with 50 mg/kg sodium pentobarbital (Nembutal). Cannula placements were subject to histological verification.

Self-administration procedures. To aid acquisition of self-administration responding, subjects were initially trained to lever press for food reinforcement on a continuous reinforcement schedule. Once stable responding was achieved (more than 100 lever presses per day, for two days), silastic jugular catheters and guide cannula were implanted (see the Surgical Procedures section for details). After implantations were completed, animals were individually housed in a self-administration cage contained in a sound-attenuated chamber. Animals remained in the cage for the duration of the experiment under reversed 12-hour lighting conditions (lights off at 9 a.m.). Animals were allowed to lever press for cocaine administration over a three-hour period per day (six days a week) on a continuous reinforcement schedule (commencing two hours after the lights were turned off). Each lever press delivered a 0.1 ml infusion of cocaine over a five-second period. Cocaine (0.5 mg/infusion) was dissolved in sterile 0.9% saline. Cocaine dose was not corrected for body weight in self-administration animals, because daily changes in solution can introduce lethal amounts of air in the animals bloodstream. A 0.5 mg/infusion dose corresponds to a dose of approximately 1.5 mg/kg/infusion. Following each infusion, levers were deactivated for 20 seconds to prevent overdose from continuous infusion. Microdialysis procedures were implemented once stable responding was achieved. Stable responding was defined as three days/trials in which the number of lever presses did not deviate by more than 10% for any individual trial.

Microdialysis procedures. Two microdialysis procedures were used in the present series of experiments. In experiments with anesthetized animals an on-line microdialysis procedure was used, in which the sample ran directly from the rat brain to a HPLC injector valve (2). An off-line procedure was used in behaving

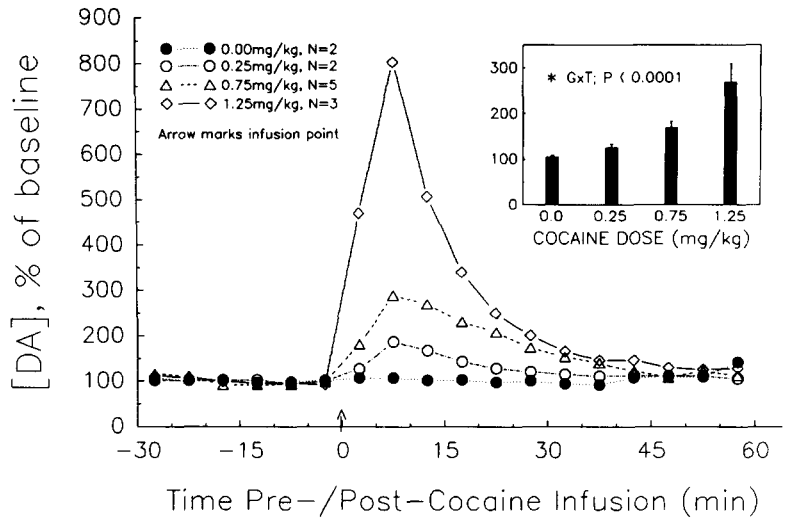

FIG. 1. The dose-dependent effects of a single intravenous infusion of cocaine on the extracellular concentration of DA in the N ACC. Data were obtained from anesthetized animals. Histogram illustrates the % of baseline DA concentration averaged across time (from −5 to 60 min) for each cocaine dose. The asterisk refers to a significant group by time (G×T) interaction revealed by a two-way ANOVA (see text for details). The average basal concentration of DA was 41.2 ± 10.6 nM. Vertical bars represent the SEM.

animals (extracellular fluid samples were manually injected into the HPLC injector valve). On-line procedures are not effective in animals which self-administer cocaine, because rotational hyperactivity serves to twist, and thus prevent flow through the microdialysis lines. The use of a liquid swivel on a dialysis outflow line is inappropriate with slow flow rates, because dead volume is created which substantially reduces sensitivity and accuracy.

Prior to insertion of microdialysis probes into either anesthetized or behaving animals, a DA standard was perfused through the probe to establish proper functioning of the probe. After testing, the probe was rinsed in artificial CSF and either stereotaxically lowered into the N ACC of anesthetized animals, or inserted into the guide cannula of behaving animals. Damage created by insertion of a dialysis probe produces a large short-term increase in extracellular DA levels. Therefore, cocaine administration was allowed only after DA concentrations had stabilized for at least a one-hour period (2–3 hour wait for anesthetized animals, 1–2 hour wait for behaving animals). The flow rate for on-line dialysis was 210 nl/min, and 0.5 μl samples were assayed in five-minute intervals. The flow rate for off-line dialysis was 300 nl/min, and 0.5 μl samples were assayed in 15-minute intervals. Approximately 40% recovery was obtained with the two mm probe at 210 and 300 nl/min flow rates. Preparation of artificial CSF, postcalibration procedures, and chromatographic procedures have been previously reported (2,18).

Pharmacodynamic calculations. The response profile of extracellular DA concentration for a single intravenous injection of cocaine was obtained from the following equation:

$$[DA] = (Ak_1/(\alpha - \beta))(\exp(-\beta t) - \exp(-\alpha t)) \quad (1)$$

In the above equation (31), $\alpha = 0.583$ min^{-1}, $\beta = 0.0825$ min^{-1}, and $k_1 = 0.378$ min^{-1}. These constants were obtained by curve fitting using simplex optimization with data expressed as a percent of baseline. This form of the equation was chosen to allow comparison with work on the pharmacokinetics of cocaine (manuscript in preparation). Data were obtained from the DA concentration detected in anesthetized animals following a single intravenous infusion of cocaine (0.25, 0.75, 1.25 and 1.5 mg/kg). The 1.5 mg/kg data were obtained from Hurd *et al.* (11). The DA response factor (A; = 59) for chronic self-administration rats was obtained by using the above constants in fitting the data obtained from cocaine self-administration animals cited in the present text. The calculated DA concentration in self-administration animals was obtained by linear superposition of single infusion responses at the infusion times produced by self-administration animals of the present study.

RESULTS

All microdialysis probes were verified by histology to be located in the N ACC. The active area of each probe was anterior to the central lateral septum, medial to the anterior commissure, and dorsal to the preoptic area.

The extracellular concentration of DA in the N ACC was observed to increase in a dose-dependent manner following a single intravenous infusion of cocaine in anesthetized animals (Fig. 1). A two-way analysis of variance (ANOVA) with repeated measures over time indicated that the intravenous infusion of different doses of cocaine (0.0, 0.25, 0.75 and 1.25 mg/kg) had differential effects on DA concentrations over time, $F(36,96) = 2.83$, $p<0.0001$. A single intravenous infusion of cocaine (0.25, 0.75 and 1.25 mg/kg) produced a maximum increase in the extracellular concentration of DA within 10 minutes. For the largest dose (1.25 mg/kg), DA increased to 800% of the baseline concentration. The DA concentration was then observed to fall, and return to basal levels within a 60-minute period.

An example of the effects of repeated infusions of cocaine on the DA concentration in the N ACC, is depicted in the top panel of Fig. 2. When cocaine was administered in a schedule which was based on the schedule produced by self-administration animals (i.e., one infusion of 0.75 mg/kg/infusion of cocaine every five minutes) (13); the DA concentration in the N ACC rapidly increased, and stabilized during the cocaine administration period.

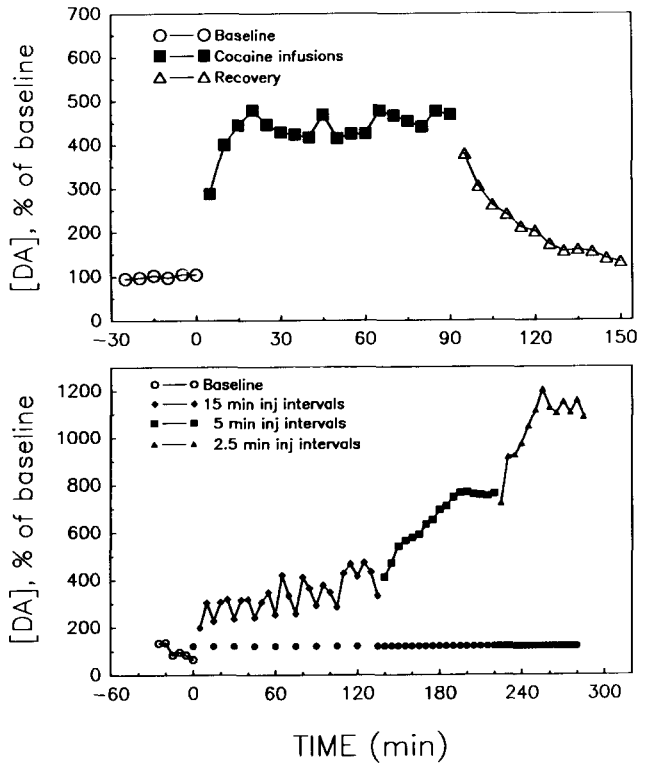

FIG. 2. Top panel illustrates the effects of a five-minute cocaine administration schedule (0.75 mg/kg/infusion) on extracellular DA concentrations in the N ACC. Data was obtained from an anesthetized animal. Bottom panel shows changes in the extracellular concentration of DA in the N ACC during three different schedules of intravenous cocaine administration in an anesthetized animal (0.75 mg/kg/infusion). The time points at which cocaine injections were given are indicated by solid circles.

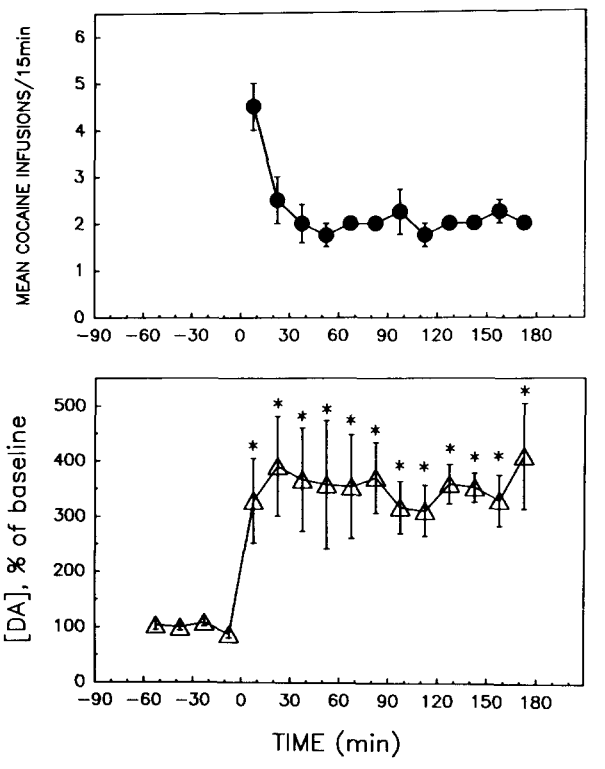

FIG. 3. The mean number of infusions (lever presses), and the concentration of DA in the nucleus accumbens during cocaine self-administration (0.5 mg/infusion; N = 4). Top panel depicts the mean number of cocaine infusions (lever presses) that occurred in successive 15-min intervals. Bottom panel illustrates the extracellular concentration of dopamine that is maintained by the titrated cocaine infusion schedule depicted in the top panel. Asterisks indicate a significant ($p<0.01$) increase from the DA concentration at the zero time point as revealed by Newman-Keuls post hoc comparisons. The mean basal concentration was 21.9 ± 0.97 nM. Vertical bars represent SEM.

The effect of different schedules is shown in the bottom panel of Fig. 2 (one infusion every 15, 5 or 2.5 minutes). A fifteen-minute infusion interval produced a noticeable increase in DA, but less than the 5-minute infusion interval. Concentrations of DA were observed to rise and fall within each 15-minute infusion interval. When the infusion frequency was increased to once every 2.5 minutes, DA concentrations rose substantially above the level maintained by a five-minute infusion schedule. The average percent increase from the basal DA concentration was 333%, 639%, and 1049%, for 15-, 5- and 2.5-minute infusion schedules, respectively. These data indicate that stable DA concentrations maintained by a five-minute cocaine infusion schedule do not occur because ceiling effects prevent DA concentrations from reaching higher levels. In addition, data obtained during the 15-minute infusion schedule indicate that the extracellular concentration of DA in the N ACC can change substantially within a five-minute period (Fig. 2; bottom panel). The DA concentration in the N ACC is greatly affected by the time interval between cocaine infusions.

The mean number of lever presses, and the concentration of DA in the N ACC during cocaine self-administration, are depicted in Fig. 3. An initial burst of responding (loading dose) was followed by lever pressing rates that were consistent over time (top panel, Fig. 3). The extracellular concentration of DA in the N ACC was observed to rapidly increase and stabilize at a level above the basal concentration (bottom panel, Fig. 3). The mean extracellular concentration of DA during cocaine self-administration was 78 nM, which reflects a 354 ± 8% increase over the 22 nM basal concentration. The mean DA concentration that occurred during the three-hour self-administration period for each of the four animals was 462 ± 30, 333 ± 17, 425 ± 26, and 186 ± 18 percent of the basal DA concentration. A one-way ANOVA with repeated measures over time indicated a significant difference in DA concentrations over time, $F(12,36) = 3.08$, $p<0.005$. Newman-Keuls post hoc comparisons indicated that all mean DA concentrations observed during cocaine self-administration were significantly above the mean basal value ($p<0.01$ in all cases; the basal value used in analyses was the value obtained from the last sample prior to cocaine administration). These results indicate that well titrated responding for cocaine can increase, and maintain extracellular DA concentrations in the N ACC at level that is more than three times the basal concentration.

Animals had a mean of 10 days/trials of self-administration experience prior to dialysis. Each animal respectively received 10, 5, 10 and 15 days of cocaine self-administration experience. Thus, the 354% increase reported above represents a DA level which can be obtained in animals which have experienced 5–15 days of cocaine self-administration. A low correlation was observed between DA levels and training time ($r = -.5$).

The present procedures only provide a measure of the mean DA concentration during a 15-minute interval in which animals respond for cocaine approximately twice (Fig. 3). The pharmacodynamics of cocaine suggest that DA concentrations rise and fall following each infusion of cocaine. Therefore, pharmacokinetic

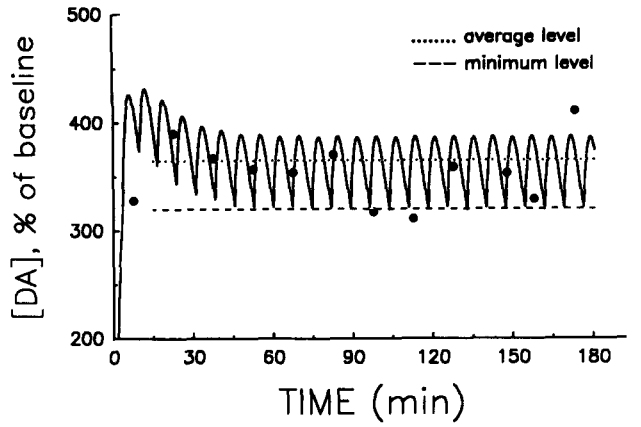

FIG. 4. The calculated DA profile and experimental data of the extracellular concentration of DA during cocaine self-administration. The calculated profile (solid line) was obtained from the average titration schedule produced by all self-administration animals of the present study using equation 1. Average titration schedules of 1.66 min/inj for 0–5 min, 6.66 min/inj for 5–15 min and 7.25 min/inj for 15–180 minutes of the self-administration period were used in calculation of the DA profile. Experimental DA concentrations (from Fig. 3) are shown as solid circles. The dashed and dotted lines indicate the minimum and average level, respectively.

calculations were used to estimate the profile of DA concentration which occurred within interresponse intervals during cocaine self-administration. The rate constants were based on the dopaminergic response to a single infusion of cocaine in anesthetized animals. The response factor was based on the observed level of DA in the self-administration animals. These calculations provide a general estimate of the fluctuation that occurs in DA concentrations during cocaine self-administration. The calculated and experimental DA concentration for the animals that self-administered cocaine is depicted in Fig. 4. Following each infusion of cocaine, DA uptake is inhibited, and a corresponding increase in extracellular DA levels occurs. The concentration of DA then begins to fall as cocaine is metabolized and DA reuptake increases.

DISCUSSION

The present results indicate that the extracellular concentration of DA in the N ACC increases in a dose-dependent manner following a single intravenous infusion of cocaine and that titrated responding during intravenous cocaine self-administration results in an elevated DA concentration. This elevated level is well above the basal DA concentration and is relatively stable over time. The increased level of DA in the extracellular fluid does not appear to be limited by ceiling effects, because the DA concentration can increase beyond the 354% increase depicted in Fig. 3 (see Fig. 2). Data in these panels further indicate that a steady state response to multiple infusions of cocaine is rapidly established.

Figures 2 and 3 indicate that the elevated levels of DA actually represent averages of the fluctuating DA concentration that occurs after each infusion of cocaine. Evidence that fluctuations in DA concentrations occur between infusions is shown in the fifteen-minute infusion data depicted in the bottom panel of Fig. 2. A five-minute observation period is short enough relative to the infusion interval to detect the fluctuations. With shorter infusion intervals or longer periods of sample collection, these fluctuations are not observable. Thus, with a fifteen-minute sample collection period, only the average DA concentration is detected in the self-administration data of Fig. 3.

The fact that cocaine produces an increase in the concentration of DA, and that regular rates of infusion maintain oscillating levels of DA, is not surprising. Cocaine is well acknowledged to inhibit the reuptake of DA (4,25), and the pharmacokinetics of drug (cocaine) administration predict regular fluctuations around a stable mean concentration of cocaine during a multiple infusion schedule (31). Present results suggest that the level of DA is tracking the level of cocaine, as has been shown in earlier studies (11,18) (see the 15-minute infusion data in the bottom panel of Fig. 2).

The present data demonstrate that the concentration of DA in the N ACC is increased and maintained at a high level during cocaine self-administration. The standard errors of the mean (SEMs) depicted in Fig. 3 reflect individual differences between animals rather than variations within animals. Current findings indicate that individual animals may maintain different DA concentrations in the N ACC. Although between subject means can vary substantially, DA concentrations within subjects over time are remarkably stable. This is reflected in the very small SEMs for individual animals (462 ± 30, 333 ± 17, 425 ± 26, and 186 ± 18 percent of the basal DA concentration for each animal respectively). These results indicate that individual animals maintain a stable concentration of DA in the N ACC during cocaine administration. More data is needed to provide a useful between-subject quantification of the DA level maintained during cocaine self-administration.

Self-selection of a particular rate or pattern of responding implies that the effects produced by the given rate of drug delivery are optimally reinforcing. The results of the lower panel of Fig. 3 indicate that an elevated level of DA is produced in the N ACC for the rate of responding reported in the upper panel of Fig. 3. Whether this elevation in DA is causally related to the self-administration behavior or only a correlate remains to be established.

Blockade of the reuptake of DA by cocaine will presumably produce a corresponding increase in the extracellular concentration of DA in all areas of the brain which contain DA terminals. In turn, ongoing neurochemistry in a multitude of other brain regions will be affected by an increase in extracellular DA levels. Therefore, the involvement of brain regions other than the N ACC in the mediation of cocaine self-administration behavior cannot be ruled out. However, substantial evidence exists in support of a primary role for DA in the N ACC in the mediation of the reinforcing effects of cocaine, and psychomotor stimulants in general (15, 20, 26, 27). Dopaminergic effects in the medial prefrontal cortex (PFC) have also been implicated in the reinforcing effects of cocaine (8–10). Demonstrations that lesions of DA terminals in the N ACC but not in the PFC attenuate cocaine self-administration behavior emphasize the importance of the N ACC in mediating self-administration behavior (16, 26, 27).

Although reinforcing effects of cocaine are thought to be primarily mediated by DA in the N ACC, a number of other factors undoubtably influence cocaine self-administration behavior. For example, aversive effects may be produced as cocaine intake is increased. Additionally, effects that occur in areas other than the N ACC may play a role. The results in Fig. 3 indicate that the titration of responding for cocaine administration maintains an elevated level of DA in the N ACC. The self-selected titration pattern indicates that cocaine-induced reinforcement is maximal. Specific fluctuations in the magnitude of reinforcement may mediate responding; however, fluctuations in heart rate, blood pressure or body temperature may also affect responding. Thus, deviations from the level of reinforcement produced by DA in the N ACC may or may not be the complete physiological signal that initiates responding for drug administration.

Yokel and Pickens (37,40), and Pickens *et al.* (24) have suggested that if the concentration of stimulants in the body fall below some "minimal level" animals will reinstate responding for drug administration. Wise and associates (38,34) have implied a DA threshold of reward by proposing that the reinforcing properties of all stimuli are primarily mediated by DA release in the N ACC. Now with the use of in vivo microdialysis procedures neurochemical events that occur during cocaine self-administration can be experimentally quantified.

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