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The effect of nitric oxide synthesis inhibition on intravenous cocaine self-administration

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Abstract

Adult male rats were implanted with intravenous catheters. After a minimum of 10 days recovery from surgery, rats were trained to intravenously self-administer cocaine (1 mg/kg/infusion) during 3-h test sessions. The nitric oxide synthase (NOS) inhibitor $N\omega$ -nitro-L-arginine methyl ester hydrochloride (L-NAME) was used to determine the effect of nitric oxide (NO) synthesis inhibition on cocaine self-administration. A 5-day protocol was used and on Days 2 and 5, an intraperitoneal injection of L-NAME (0, 3, 30, 300 mg/kg) was administered 45 to 60 min into a 3-h test session. One to two hours following L-NAME administration, there was a dose-dependent decrease in the amount of self-administered cocaine and an increase in the interresponse time (IRT) between successive cocaine injections. L-NAME appeared to prolong the rewarding effect of cocaine possibly through a pharmacokinetic action. © 2001 Elsevier Science Inc. All rights reserved.

Keywords: Cocaine; L-NAME; Nitric oxide; Nitric oxide synthesis inhibition; Psychomotor stimulants; Stimulant self-administration

1. Introduction

Cocaine is a highly addictive drug that produces potent reinforcing effects in both humans and laboratory animals. Cocaine binds to the dopamine transporter and pharmacologically blocks dopamine reuptake in the nucleus accumbens to produce its reinforcing action (reviewed in Bozarth, 1986, 1987, 1989; Fibiger, 1978; Kuhar et al., 1995; Wise, 1978; Wise and Bozarth, 1987). The site of cocaine binding on the dopamine transporter has been suggested to be the "cocaine receptor" related to substance abuse (Ritz et al., 1987, 1988). Supporting this hypothesis are positron emission tomography (PET) data showing that cocaine's occupancy on the dopamine transporter and the psychological effects induced by cocaine show a similar time course (Fowler et al., 1989).

Changes in the magnitude of cocaine reinforcement can be directly assessed with the intravenous self-administration (IVSA) method. Animals allowed to intravenously selfadminister cocaine typically display stable patterns of drug intake characterized by regularly spaced infusions (i.e., stable interinfusion intervals; Pickens, 1968; Pickens and Thompson, 1968; Wilson et al., 1971; Yokel, 1987). Also, an inverse relationship exists between the unit dose of cocaine and the number of self-administered drug injections (Pickens, 1968; Pickens and Thompson, 1968; Wilson et al., 1971). That is, increasing the unit dose (i.e., the drug dose delivered per infusion) of cocaine produces a corresponding decrease in the number of self-administered drug injections. Conversely, decreasing the unit dose of cocaine produces an increase in the number of self-administered drug injections. When cocaine infusions are terminated by turning off the infusion pump or when saline is substituted for cocaine in the infusion syringe, animals display an extinction pattern consisting of a response burst followed by a cessation of responding (Pickens, 1968; Pickens and Thompson, 1968).

Predictable changes in the patterns of cocaine self-administration are also displayed when animals are pretreated with either a dopamine agonist or antagonist (for a review, see Yokel, 1987). Animals pretreated with a dopamine agonist (e.g., amphetamine) display a dose-dependent decrease in cocaine self-administration (Wilson and Schus-

Abbreviations: ANOVA, analysis of variance; BSR, brain stimulation reward; CNS, central nervous system; EDRF, endothelium-derived relaxing factor; FR-1, fixed ratio-1; IRT, interresponse time; IVSA, intravenous self-administration; NO, nitric oxide; NOS, nitric oxide synthase; L-NAME, $N\omega$ -nitro-L-arginine methyl ester hydrochloride; PET, positron emission tomography

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ter, 1973), while animals pretreated with a dopamine antagonist (e.g., pimozide) exhibit one of two different patterns of cocaine self-administration. Animals pretreated with a low to moderate dose display increased rates of cocaine selfadministration as they attempt to overcome the pharmacological blockade. However, at higher doses, animals display an extinction-like pattern similar to the pattern observed when saline is substituted for cocaine in the infusion syringe (De Witt and Wise, 1977). Thus, the stable and predictable patterns of cocaine self-administration can be used to determine if an experimental manipulation alters cocaine's reinforcing effect.

Nitric oxide (NO) is a highly reactive gas that can easily penetrate cell membranes by diffusion and it may represent a new type of retrograde neurotransmitter (Snyder and Bredt, 1992). NO-containing neurons have been identified in the mesolimbic brain area involved in cocaine reinforcement (i.e., nucleus accumbens; Vincent and Kimura, 1992). In addition, several in vitro and in vivo studies have shown that NO modulates dopamine activity. Nitric oxide synthase (NOS) inhibitors have been shown to attenuate evoked dopamine release (Bowyer et al., 1995; Hanbauer et al., 1992; Zhu and Luo, 1992) and to affect dopamine transporter function (Pogun and Kuhar, 1994; Pogun et al., 1994).

Additional studies have shown that NOS inhibitors block the development of sensitization to cocaine's locomotorstimulating effect (Kim and Park, 1995; Pudiak and Bozarth, 1993) and to cocaine's convulsive and lethal effects in animals (Itzhak, 1993). Furthermore, NOS inhibition has been shown to block the development of a conditioned place preference in cocaine-treated animals (Kim and Park, 1995). These data suggest that NO may alter cocaine's reinforcing effect through its modulation of dopamine activity and they strongly support a role for NO's involvement in cocaine reinforcement.

This experiment assessed NO's involvement in cocaine reinforcement and used the NOS inhibitor $N\omega$ -nitro-L-arginine methyl ester hydrochloride (L-NAME) to inhibit NO production. The effect of NO synthesis inhibition on cocaine reinforcement was examined in laboratory animals allowed to intravenously self-administer cocaine. Both changes in the pattern and the amount of self-administered cocaine were used to determine if L-NAME treatment significantly altered cocaine's reinforcing effect.

2. Methods

2.1. Animals

Experimentally naive, male, Long–Evans rats (Harlan Sprague–Dawley, Indianapolis, IN) weighing between 350 and 375 g were individually housed with food and water available ad libitum. The drinking water contained 10-14 ppm chlorine and was acidified to pH 2.5 to 2.8. The animal colony was maintained at a constant temperature (22 ± 2 °C)

and humidity ($50 \pm 5\%$ RH) with a 14-h light/10-h dark illumination cycle. All behavioral testing was conducted during the light phase of the light/dark cycle between 1000 and 1600 h.

2.2. Drugs

L-NAME was purchased from Sigma (St. Louis, MO). L-NAME was prepared daily prior to testing and was dissolved in sterile physiological saline. Cocaine hydrochloride, obtained from the National Institute on Drug Abuse (Rockville, MD), was dissolved in sterile physiological saline, sterilized by filtration (0.22 µm filter), and stored at room temperature. L-NAME (3, 30, or 300 mg/kg) was administered intraperitoneally and cocaine hydrochloride (1 mg/kg/injection) was self-administered intravenously. All drug dosages refer to the drug salts. Intravenous catheters were flushed daily with heparinized saline (0.2 to 0.4 ml iv) before testing and with Penicillin G (0.4 ml iv) dissolved in heparinized saline after testing. Each milliliter of Penicillin G solution contained 10 IU of heparin to prevent blood coagulation in the catheter and 50,000 IU of Penicillin G to retard infection.

2.3. Apparatus

Self-administration behavior was tested in chambers $(25 \times 37 \times 28 \text{ cm high})$ made of metal and Plexiglas with stainless steel tubular floors. Each chamber was housed in a dimly illuminated, sound-attenuating chamber with exhaust ventilation. The self-administration chambers contained two levers and a light flexible infusion line that allowed unrestricted movement of the animal during behavioral testing. One lever was located on one wall and a second lever was located on the opposite wall. Pressing one lever activated a motor-driven syringe pump that delivered a 0.25-ml injection over 30 s. Lever pressing during the injection interval did not produce a second injection, but lever pressing immediately after completion of the injection interval produced another drug injection. A light located above this lever was activated during the drug infusion. A second lever was an inactive lever and pressing it did not deliver an injection. This lever provided a measure of the animal's general activity and of accidental lever contacts.

2.4. Catheter surgery

Following a minimum of 7 days habituation to the animal colony, each animal was surgically implanted with a chronically indwelling intravenous catheter. Each Silastic catheter (Dow Medical Grade Tubing) was 10 cm in total length and had an outer diameter of 1.2 mm and an inner diameter of 0.6 mm. The insertion tip of each catheter was beveled and a small piece of Silastic tubing (2.2 mm o.d. \times 1.0 mm i.d.) was attached around the catheter at approximately 4.2 cm from the insertion tip. The catheter

was then attached to a curved 22-gauge stainless steel tube. A piece of Polyolefin heat shrink tubing was slipped over the area where the catheter and stainless steel tube overlapped and heat was applied until a tight seal formed. Prior to surgical implantation, each catheter was pressure tested for any leaks or defects.

Rats were anesthetized using sodium pentobarbital (60 mg/kg ip) supplemented with atropine sulfate (0.4 mg/kg ip) and Penicillin G (100,000 units im). The jugular vein was located by palpating the point of curvature (V-shaped) on the right side of the animal's neck. The point of curvature was used to determine the placement of an incision (0.5 to1.0 cm) in the animal's neck. After the incision was made, fatty and connective tissue were cleared away by blunt dissection until the jugular vein was located. A pair of straight hemostats was then used to isolate the jugular from the attached connective tissue beneath the vein. Two pieces of surgical suture (4.0 Polyamide sterile suture) were then placed underneath the vein. One suture was placed near the top portion of the exposed vein, and the other suture was placed near the lower portion of the exposed vein. The top suture was tightened to ligate the top portion of the vein. Once the vein was ligated, the jugular vein was raised by holding the top ligature and a snip was made with a pair of iris scissors in the middle to lower portion of the exposed vein. An autoclaved Silastic catheter was then inserted 4.2 cm into the incision and the bottom suture was tightened around the catheter.

To assure the catheter was in the jugular vein and to assure no leaks occurred at the point of insertion, blood was aspirated from the catheter four to five times and approximately 0.6 ml of heparin solution was then infused. A minuscule amount of cyanoacrylate adhesive (Thick Gel Super Glue, Super Glue, Hollis, NY) was then applied onto the sutures tightened around the catheter. Next, a small subcutaneous tunnel was made up the back of the animal's neck by performing blunt dissection with a pair of straight hemostats. The catheter was drawn through this small tunnel and it exited at the back of the animal's neck. The wound was then sutured and Neosporin ointment was applied to the external surface of the wound. The portion of the catheter that contained the curved stainless steel tube was attached to the animal's skull with dental acrylic and was anchored by stainless steel screws. The stainless steel tube provided a convenient connection for the intravenous infusion line during self-administration testing. At the completion of surgery, Penicillin G solution was infused (0.4 ml iv) into the catheter line and a cap made from melted Tygon tubing was placed on the stainless steel tube to prevent air from entering the catheter line.

2.5. Experimental procedure

Following a minimum of 10 days recovery from the surgical procedure, animals were allowed to self-administer intravenous cocaine (1 mg/kg/injection) using a fixed-ratio

schedule (FR-1). Testing was conducted 3 h per day, 5 days per week with 2 days of no testing intervening between each 5-day block of testing. Animals were allowed to stabilize their drug intake (i.e., approximately 2 weeks) before any experimental manipulation was introduced. Drug intake was considered stable when animals displayed nearly identical drug intake across consecutive test sessions (i.e., a minimum of six test sessions). A baseline was computed for each animal by averaging 3 days of drug intake prior to L-NAME treatment. If cocaine intake was not within 10% of the animal's baseline on the day preceding a challenge injection, the injection was postponed until the next scheduled injection day. Also, if drug intake was irregularly high or low during the first 45 min of the test session, the injection was postponed until the next scheduled injection was postponed until the next scheduled injection was

Once animals (n = 10) showed stable drug intake, a 5-day protocol using an FR-1 schedule was initiated. Day 1 served as a warm-up day; on Day 2 a challenge injection was administered; on Days 3 and 4 testing continued; and on Day 5 another challenge injection was administered. On Days 2 and 5 testing was suspended for 1 to 2 min and animals were administered an L-NAME injection (3, 30, 300 mg/kg ip) 45 to 60 min into the 3-h test session (Fig. 1). All challenge injections were separated by a minimum of 72 h, and all doses were administered in a counterbalanced order. A single daily priming injection was administered by the experimenter if an animal did not self-administer cocaine within the first 15 min of the test session. Intravenous catheters were flushed with 0.4 ml of heparinized saline prior to each test session and were flushed with 0.4 ml of Penicillin G solution following the test session. All animals had their catheters flushed with 0.4 ml of Penicillin G solution on days of no testing.

2.6. Statistical analysis

An analysis of variance (ANOVA) was used to determine if cocaine intake was significantly altered following L-NAME administration. Mean cocaine intake was computed by averaging the number of self-administered cocaine injections made during the third hour of testing at each dose of L-NAME or vehicle. Pairwise comparisons (i.e., a Newman–Keuls' test) were then used to detect statistical



Fig. 1. A time line of the test session. The figure shows when L-NAME was administered during the 3-h test session. The analysis used data from the time period 1 to 2 h following L-NAME administration (i.e., third hour of testing).

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Fig. 2. Response patterns seen following saline and each L-NAME dose for a typical subject during the 3-h test session. Physiological saline or L-NAME was injected 45 to 60 min into the test session.

differences among the treatment conditions. A separate ANOVA was used to determine if the interresponse times (IRTs) between successive cocaine injections were altered following L-NAME administration. The mean time between successive cocaine injections was computed by subtracting the infusion times of successive cocaine injections made during the third hour of testing to yield an IRT. The IRTs were then averaged for the group of animals at each dose of L-NAME and vehicle. Once again, pairwise comparisons (i.e., a Newman–Keuls' test) were used to detect statistical differences among the treatment conditions.

3. Results

3.1. Drug intake

The NOS inhibitor L-NAME significantly altered the reinforcement profile of intravenous cocaine. Fig. 2 shows the response patterns for each treatment condition for a typical subject. For statistical comparisons, the effect of L-NAME on self-administered cocaine intake during the third hour of testing was used (Fig. 3). L-NAME treatment

decreased mean cocaine intake compared to saline. Furthermore, the observed decrease in cocaine intake following L-NAME administration was dose-dependent. An ANOVA used to examine drug intake across the four treatment conditions revealed that L-NAME produced a significant decrease in cocaine intake during the third hour of testing (i.e., 1 to 2 h following L-NAME administration) [F(3,27)=13.154, P<.001]. A Newman–Keuls' test revealed that animals administered L-NAME displayed decreased drug intake compared to saline-treated animals (*P*'s<.05). The decreased drug intake produced by the 3- and 30-mg doses of L-NAME was significantly different from the 300-mg dose of L-NAME (*P*'s<.05); the 3- and 30-mg doses of L-NAME were not significantly different from one another (*P*>.05).

3.2. Interresponse times

Changes were also observed in the IRTs between successive cocaine injections following L-NAME administration. Fig. 3 illustrates the effect of L-NAME treatment on the mean time (min) between self-administered cocaine injections during the third hour of testing. L-NAME treatment increased the mean time between successive cocaine injections compared to vehicle [F(3,27)=11.831, P<.001]. The highest dose of L-NAME produced a 60% increase in the time between self-administered cocaine injections.

Event records shown in Fig. 4 display individual patterns of cocaine self-administration for animals during the third hour of testing following a 300-mg injection of L-NAME. Each tick on the event record depicts the occurrence of a self-administered cocaine injection. All animals exhibited stable self-administration patterns as demonstrated by the evenly spaced cocaine injections. Also shown is the con-



Fig. 3. The effect of L-NAME on cocaine intake (open circles) and on IRTs (filled circles) during intravenous cocaine self-administration. The figure shows the mean cocaine intake (mg/kg/h) for the period 1 to 2 h post-L-NAME injections and the mean time (min) between successive cocaine injections. The NOS-inhibitor produced a dose-dependent reduction in cocaine intake but produced a dose-dependent increase in IRTs. The highest dose of L-NAME produced a 60% increase in the time between self-administered injections (IRTs).



Fig. 4. Event records for individual subjects self-administering cocaine after receiving the 300-mg/kg L-NAME dose. Each record shows the pattern of cocaine intake during the third hour of testing used in the data analysis.

siderably lengthened IRTs that L-NAME-treated animals displayed between successive cocaine injections.

Pairwise comparisons (i.e., a Newman–Keuls' test) revealed that animals administered 30- or 300-mg of L-NAME exhibited more time between successive cocaine injections than animals administered saline (P's < .05); the 3-mg dose of L-NAME failed to produce significantly different IRTs from saline (P>.05). Animals injected with 300-mg of L-NAME displayed longer IRTs than animals administered either the 3- or 30-mg doses of L-NAME (P's < .05); the 30-mg dose failed to produce significantly longer IRTs than the 3-mg dose of L-NAME (P>.05). The dose-dependent increase and the stable duration of the IRTs within the L-NAME test sessions suggest that animals are regulating their drug intake and further suggest that NOS inhibition significantly altered cocaine reinforcement.

4. Discussion

4.1. The reinforcement profile of cocaine

The present findings show that L-NAME pretreatment significantly alters the reinforcement profile of intravenous cocaine. Following L-NAME administration, animals showed a dose-dependent decrease in the mean number of self-administered cocaine injections and a dose-dependent increase in the mean time between successive cocaine injections. The dose-dependent nature of this effect suggests that L-NAME treatment does not decrease drug intake through a motoric or disruptive side effect. Furthermore, animals periodically observed during the L-NAME test sessions failed to exhibit any signs of behavioral disruption. These data, in conjunction with previous findings showing that animals administered a 300-mg/kg injection of L-NAME make approximately 80 lever presses per minute for electrical brain stimulation (Bozarth et al., 1994), strongly suggest that the decreased drug intake observed following L-NAME administration is not the result of a motoric or disruptive side effect. Rather, the pattern of cocaine self-administration seems to closely resemble the self-administration patterns exhibited by animals injected with a dopamine agonist (e.g., amphetamine). Thus, from the observed patterns of decreased cocaine intake and increased IRTs between successive cocaine injections, it can be inferred that L-NAME pretreatment prolongs the reinforcing effect of intravenous cocaine.

The present finding that NOS inhibition prolongs cocaine's reinforcing effect is inconsistent with an earlier finding showing that NOS inhibition prevented the development of a cocaine-induced conditioned place preference (Kim and Park, 1995). Unlike the Kim and Park (1995) study, animals used in this experiment were administered the NOS inhibitor only after the behavior (i.e., self-administration) had been learned. This may be an important variable since several studies have shown that NOS inhibitors block several types of learning (e.g., cellular, spatial learning; Barinaga, 1991; Hölscher et al., 1995). In addition, the NOS inhibitor (i.e., $N\omega$ -nitro-L-arginine) used in the Kim and Park study also produces potent vasoconstrictor actions. Thus, it is possible that a vasoconstrictor action may have blunted cocaine's initial rewarding impact and diminished cocaine's subjective effect, thereby blocking the development of a cocaine-induced conditioned place preference. However, the possibility still remains that the apparent discrepancy is simply due to the use of a different NOS inhibitor or to methodological differences.

4.2. Dopamine activity

It is unlikely that L-NAME altered cocaine's reinforcing effect through a dopaminergic action. Previous findings have shown that L-NAME fails to significantly affect frequency thresholds for brain stimulation reward (BSR), indicating that L-NAME does not modulate dopamine in the brain dopamine system that mediates the rewarding effects of BSR (Bozarth et al., 1994). Furthermore, L-NAME administration failed to attenuate cocaine's threshold-lowering effect in BSR (Bozarth et al., 1994). The brain dopamine system that is electrically activated by BSR is also pharmacologically activated by the psychomotor stimulants (e.g., cocaine). Thus, if L-NAME modulated dopamine activity in this brain region, it would be expected that L-NAME would have altered frequency thresholds in BSR and, secondly, that L-NAME would have altered cocaine's threshold-lowering effect.

It is also unlikely that L-NAME exerted a significant effect on dopamine transporter function since previous data have shown that NOS inhibition increases dopamine uptake (Pogun and Kuhar, 1994). Experimental manipulations that abate dopamine activation (e.g., dopamine antagonists, dopamine-depleting lesions, increased dopamine reuptake) diminish the rewarding effects of intravenous cocaine and produce patterns of either increased drug intake or extinction-like responding (Roberts and Zito, 1987; De Witt and Wise, 1977; see also Yokel, 1987) and therefore decrease the IRTs between successive drug injections. The selfadministration patterns exhibited by L-NAME-treated animals do not resemble the previously mentioned patterns and are therefore inconsistent with a diminution of cocaine's reinforcing effects.

4.3. A pharmacokinetic manipulation

A viable alternative that may explain L-NAME's apparent enhancement of cocaine reward is a pharmacokinetic manipulation that prolongs cocaine's reinforcing effect. Drugs are delivered to brain tissue via blood circulating through the internal carotid arteries and the vertebral arteries (Chien, 1985). The regulation of cerebral blood flow can be affected by hypertensive states that induce vasoconstriction of the cerebral arteries and arterioles (Chien, 1985).

NO, formerly known as endothelium-derived relaxing factor (EDRF), has a prominent role in the regulation of vascular tone, local blood flow, and blood pressure (Furchgott, 1996). NO stimulates guanylyl cyclase in vascular smooth muscle and increases the levels of cyclic guanosine monophosphate to induce vascular relaxation (Furchgott, 1996). Several studies have shown that blocking NO synthesis with NOS inhibitors (e.g., L-NAME) increases arteriole vasoconstriction and blood pressure and decreases cerebral blood flow (Banting et al., 1996; Gardiner et al., 1990; Tabernero et al., 1996; Togashi et al., 1992; Wang et al., 1992). Studies using L-NAME have shown that NOS inhibition significantly reduces coronary blood flow (Kostic et al., 1996) and produces intense vasoconstriction in vascular beds (Gundersen et al., 1996).

When cocaine is smoked or administered intravenously, arterial cocaine plasma levels peak within 15 s (Evans et al., 1993, 1994). This rapid rise in arterial cocaine-plasma levels is thought to produce the "rush" experienced by individuals following smoked or intravenous drug administration (Evans et al., 1993, 1994; Fischman and Johanson, 1996). Consistent with this hypothesis is the finding that individuals experience an intense "rush" within 1 to 2 min following intravenous cocaine administration (Fischman, 1984). Thus, a vasoconstrictor action that delays the abrupt onset of cocaine's initial reinforcing action may actually diminish the "rush" commonly experienced by intravenous drug users.

The same vasoconstrictor action that delays drug onset may also delay drug elimination from central nervous system (CNS) and thereby prolong cocaine's reinforcing effect. The lengthened IRTs between successive cocaine injections displayed by L-NAME-pretreated animals are indicative of a prolongation of cocaine reward. Thus, it is possible that L-NAME, through a vasoconstrictor action, prolonged cocaine's reinforcing effect by delaying drug elimination.

Consistent with L-NAME's ability to delay the abrupt onset and termination of drug action are results from Bozarth et al. (1994) showing that L-NAME pretreatment shifted the entire time-course of cocaine's facilitation of BSR to the right by 15 min. Time-course data from Bozarth et al. showed that L-NAME pretreatment delayed the time to cocaine's peak facilitation and slightly prolonged the duration of cocaine's threshold-lowering effect in BSR. However, L-NAME pretreatment did not affect cocaine's overall lowering of reward thresholds during the 60-min test session. These findings are consistent with the speculated pharmacokinetic manipulation (i.e., vasoconstrictor action) that may be produced by L-NAME pretreatment. A delay as short as a few seconds in the onset of drug action has been shown to significantly alter the reinforcement profile of cocaine (Cone, 1995). Individuals rated the subjective effects of smoked cocaine higher than the subjective effects produced by an equivalent dose of intravenous cocaine (Cone, 1995). These data demonstrate that a short delay in the onset of drug action can effectively alter the reinforcement profile of cocaine.

A pharmacokinetic manipulation of drug action may not alter a drug's overall reinforcing effect. Rather, such a pharmacokinetic manipulation of drug action may produce a subjective dampening effect by diminishing the "highs " and "lows" produced by the drug. Thus, the peak euphoric "rush" produced by cocaine may be blunted through a potent vasoconstrictor action that slows drug absorption (e.g., L-NAME's vasoconstrictor effect). A rapid elimination of cocaine from the CNS may result in an abrupt termination of drug action and it may contribute to the "crash" and withdrawal symptoms experienced by individuals following drug termination. Thus, a vasoconstrictor action that retards drug elimination and that delays the abrupt termination of drug action may effectively abate the "crash" and withdrawal symptoms experienced by individuals following drug termination.

Although this study found that L-NAME pretreatment altered the reinforcement profile of cocaine, it should be noted that L-NAME's intense vasoconstrictor action may also contribute to the circulatory complications (e.g., cardiac arrhythmia's, myocardial ischemia or infarction; cerebrovascular spasms) commonly associated with continued cocaine use. Furthermore, cognitive deficits have been documented in chronic cocaine users (O'Malley et al., 1992), and these neuropsychological deficits may be due in part to cocaine's vasoconstrictor action. Thus, a pharmacological treatment that enhances cocaine's vasoconstrictor action will most likely increase the number of complications associated with chronic cocaine use and will undoubtedly contribute to cocaine's toxicity.

Additional research is needed to identify other pharmacological agents that could be used to alter the pharmacokinetic profile of cocaine without posing any serious health risks. Such a manipulation might be exploited in conjunction with existing behavioral therapies to help break the relentless cycle of drug-taking behavior characteristic of cocaine addiction.

5. Conclusions

Pharmacotherapeutic treatments for substance dependence have generally focused on blocking the pharmacological effects of an abused drug or on abating the craving

associated with drug abstinence. These treatments have traditionally focused on the use of dopamine agonists or antagonists. Another factor that plays a critical role in substance dependence is the abrupt onset and termination of drug action. The present findings suggest a pharmacological treatment that may alter the pharmacokinetic profile of a drug might be exploited to alter a drug's subjective effects. It is suggested that a vasoconstrictor action that slows the abrupt onset of drug action may diminish the intense subjective effects characteristically produced by abused drugs. Furthermore, a mechanism that delays drug elimination from the CNS may abate the adverse feelings associated with the abrupt termination of drug action. The delay of reinforcement and possible negative contrast effects associated with continued drug use during NOSinhibition should weaken the behavioral response of drug self-administration. This may provide an enhanced window of opportunity for clinical intervention and may make existing treatment programs more effective.

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