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Effects of nimodipine and/or haloperidol on the expression of conditioned locomotion and sensitization to cocaine in rats

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Abstract. The development of classical conditioning of cocaine's locomotor effects can be dissociated from the development of sensitization to cocaine by co-administration of haloperidol, a dopamine D_2-like receptor antagonist, and nimodipine, an L-type calcium channel antagonist. The effects of these agents on the *expression* of conditioning and sensitization are described in the present report. Rats were given injections of vehicle or cocaine (10 mg/kg, IP) for 10 days before placement in a specific context in which locomotor activity was recorded. Neither haloperidol (0.05 mg/kg, IP) nor nimodipine (10 mg/kg, SC) influenced the expression of classical conditioning of cocaine's locomotor effects to the situational context on a subsequent cocaine-free test. Combined treatment of rats with both drugs did block classical conditioning with cocaine. Nimodipine, but not haloperidol, blocked the expression of behavioural sensitization to cocaine after a cocaine challenge. It is concluded that the expression of cocaine-induced classical conditioning can be pharmacologically dissociated from the expression of behavioural sensitization to cocaine. Furthermore, the effects of nimodipine and haloperidol on the expression of conditioning and sensitization are different from their effects on the development of these phenomena.

Key words: Cocaine – Nimodipine – Haloperidol – L-type Ca^{2+} channels – Dopamine receptors – Behavioral sensitization – Conditioned locomotion

The classical conditioning of the effects of psychomotor stimulants has been implicated in stimulant addiction and in the development of behavioural sensitization. Cocaine addicts exhibit strong cravings and drug-like physiological responses when presented with drug-related cues (O'Brien et al. 1988; Muntaner et al. 1989). Both the euphoric and the cardiovascular effects of cocaine are conditioned to stimuli from the drug-use context, and these conditioned responses appear to induce "cocaine cravings" (O'Brien et al. 1986; Muntaner et al. 1989). The chronic use of psychomotor stimulants such as cocaine and amphetamine can induce psychotic symptoms in humans which are almost indistinguishable from the active psychotic phase of paranoid schizophrenia (Angrist 1983). Repeated administration of low doses of stimulants results in a progressive increase in locomotor activity in animals (Robinson and Becker 1986; Weiss et al. 1989). This phenomenon (behavioural sensitization) is thought by some researchers to provide an animal model of stimulant-induced psychoses (cf Angrist 1983; Robinson and Becker 1986).

It is well documented that sensitization to the effects of a variety of psychomotor stimulants can be context specific (Post et al. 1981; Schiff 1982; Barr et al. 1983; Mattingly and Gotsick 1989; Weiss et al. 1989; Stewart and Vezina 1991), and this is typically explained as being a function of the classical conditioning of the drug effects to contextual stimuli. However, the degree to which classical conditioning of contextual cues to the effects of stimulants can account for sensitization is controversial (Robinson and Becker 1986; Martin-Iverson et al. 1988a, b; Baldo and Kelly 1991; Martin-Iverson 1991; Stewart and Vezina 1991).

The establishment of classical conditioning of the locomotor effects on amphetamine and cocaine has been shown to be blocked by pimozide (Beninger and Hahn 1983; Beninger and Herz 1986). Pimozide blocks both dopamine D_2 receptors and L-type calcium channels, with approximately equal potency. The establishment of the classical conditioning of amphetamine's locomotor effects are not blocked by haloperidol, a relatively selective antagonist for D_2 receptors that does not have appreciable action on L-type calcium channels (Martin-Iverson and McManus 1990). In addition, an L-type calcium channel antagonist, nimodipine, also failed to block the establishment of the conditioning of amphetamine-induced locomotion, but haloperidol and nimodipine given together to rats does mimic the effect of pimozide on blocking the establishment of conditioning (DiLullo and Martin-Iverson 1992b). Therefore, the effect of pimozide appears to be a function of its combined actions on both D_2 receptors and L-type calcium channels. Other work (DiLullo and Martin-Iverson 1991, 1992a) has shown that the conditioning of amphetamine's locomotor effects involves two separate processes: Ca^{2+}-dependent release of dopamine

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from vesicles (reserpine-sensitive), and Ca^{2+}-independent release from a newly synthesized dopamine compartment (sensitive to synthesis inhibition by alpha-methyl-paratyrosine).

The establishment of conditioning and sensitization to cocaine is different from these effects of amphetamine. The development of conditioning of cocaine's locomotor effects are blocked by nimodipine alone, and is unaffected by haloperidol (Reimer and Martin-Iverson 1993). On the other hand, the development of sensitization to cocaine is attenuated by either nimodipine or haloperidol (Reimer and Martin-Iverson 1993). In the present experiments, the effects of haloperidol and nimodipine on the expression of conditioning and sensitization to cocaine were investigated.

Materials and methods

Animals. Experimentally naive male Sprague-Dawley rats (250–350 g) were housed in pairs in climatically controlled room (20–22 °C, humidity = 50%). They were on a 12-h light-dark cycle (0700–1900 hours) with free access to food and water.

Drugs. Nimodipine, provided courtesy of Dr. A. Scriabine (Miles Institute for Preclinical Pharmacology, Miles Inc.), was dissolved in a solution of polyethylene glycol 400 to a final concentration of 10 mg/ml. Haloperidol was purchased from McNeil in 1-ml ampoules containing 5 mg haloperidol dissolved in a solution of methylparaben (1.8 mg), propylparaben (0.2 mg), and lactic acid. This was further diluted to a final concentration of 0.05 mg/ml haloperidol with double-distilled water. Cocaine hydrochloride, purchased from British Drug Houses, was prepared in a 10 mg/ml solution using double-distilled water.

Equipment. The locomotor activity test boxes measure 25 cm (H) × 25 (W) × 30 (L) and contain two infrared photocell assemblies placed 3 cm from the floor and 14 cm apart, equidistant from the end walls. The sensitivity of the photocells is adjusted such that only gross movements are counted. Fine movements of the head, tail, and paws are excluded. Locomotor activity was measured while the animals were in the test boxes for 60 min on each day.

Procedure. Rats in all groups ($n = 96$ for both experiments) were habituated to their home cages for 7 days before the experiment. The first experiment was an investigation of the acute effects of haloperidol and nimodipine at blocking cocaine-induced locomotion. It consisted of a single day of 60 min locomotor testing immediately after an injection of vehicle or cocaine (10 mg/kg, IP). Seventy minutes prior to cocaine treatment, the rats were given two injections, one of vehicle or haloperidol (0.05 mg/kg, IP) and one of vehicle or nimodipine (10 mg/kg, SC). The groups therefore consisted of VVV, VVC, VNV, VNC, HVV, HVC, HNV, HNC, where V = vehicle, H = haloperidol, N = nimodipine and C = cocaine.

The second (primary) experiment was composed of four phases: conditioning, classical conditioning test, retraining and sensitization test. The conditioning consisted of daily injections of cocaine (10 mg/kg, IP, $n = 48$) or vehicle ($n = 48$) in a unique environment for 10 consecutive days. Immediately following the injections on each day, the rats were placed in test boxes and locomotor activity was assessed for 1 h. After the last day of conditioning, the vehicle and cocaine groups were each divided further into four groups matched on the basis of their locomotor activity scores by calculating the average daily level of activity of each animal over the 10 days, and then by taking the four rats with the highest level of activity in each of the cocaine and vehicle groups and randomly assigning them to four groups; the four rats with the next highest activity levels were then randomly assigned to one of the four groups, and this was continued until all rats were assigned to a specific group.

After 3 days without handling or injections to allow for drug clearance, the rats were placed in the test boxes after injections with VVV, VNV, HVV or HNV, where H = haloperidol (0.05 mg/kg, IP), N = nimodipine (10 mg/kg SC), and V = vehicle (first and third injections = IP, second injection = SC), with 24 rats in each group. Each of these groups were divided further into two groups of 12, on the basis of previous treatments (i.e. vehicle or cocaine). Halperidol and nimodipine were injected 70 min before the vehicle injections; this time interval has been established in previous experiments to be appropriate for these drugs (DiLullo and Martin-Iverson 1992; Reimer and Martin-Iverson 1993). The rats were then re-conditioned with cocaine ($n = 48$) or vehicle ($n = 48$) for 3 days, following the same regimen as in the original conditioning. The sensitization test was conducted identically to the classical conditioning test except that all rats received an injection of cocaine (10 mg/kg, IP) before placement in the boxes, instead of vehicle. Rats that were conditioned with vehicle or with cocaine were therefore injected with VVC, VNC, HVC, and HNC ($n = 12$ in each of eight groups).

Statistics. The data were subjected to analysis of variance (ANOVA). In experiment 1, the results were expressed as percent of the appropriate control (e.g. the data from the HNC group was analysed as a percent of the HNV group); analysis of the raw data did not give substantially different results. In the conditioning phase, there was one independent factor: cocaine dose (two levels: vehicle or 10 mg/kg), and one repeated factor: days (ten levels). In the conditioning and sensitization tests there were three independent factors: haloperidol (two levels: vehicle or 0.05 mg/kg), nimodipine (two levels: vehicle or 10 mg/kg), and previous drug treatment (two levels: vehicle or cocaine). Locomotor activity in the retraining phase was analyzed by ANOVA with three independent factors: previous treatment (on the conditioning test day) with vehicle or haloperidol, and vehicle or nimodipine, and current treatment with cocaine (two levels: vehicle or 10 mg/kg), and one repeated factor: days (three levels).

Since ANOVA with more than two repeated measures is unreliable due to lack of homogeneity of variances or covariances when there are order effects (Vitaliano 1982), a number of multivariate tests of significance (Pillais Trace, Hotellings T, Wilks Lambda, and Roys F-test) were also conducted for terms involving this factor. Significant ANOVA results are reported in this paper only when verified by these additional tests. Significant main effects and interactions were followed by individual comparisons by the F-test for multiple comparisons (Kiess 1989). The critical level of significance was set at $P < 0.05$.

Results

The results of the acute experiment are displayed in Fig. 1. Neither nimodipine nor haloperidol significantly decreased cocaine-induced locomotion at the doses employed, but the two drugs given together blocked cocaine-induced locomotion. During the 10 days of conditioning, rats given injections of vehicle exhibited a progressive decrease in activity most marked from day 1 to day 3 (Fig. 2). Cocaine (10 mg/kg) increased locomotion, and this effect increased over the days of treatment relative to the vehicle group (Fig. 2). ANOVA revealed a significant cocaine by days interaction [$F(9,846) = 6.93$, $P < 0.001$]. The expression of cocaine-conditioned locomotion was not significantly decreased by haloperidol or by nimodipine, but the combination of the two drugs attenuated the expression of conditioned locomotion, in comparison to either the group that was conditioned with cocaine but received only vehicle injections on the test day or the group that had never received cocaine but was injected with haloperidol and nimodipine on the test

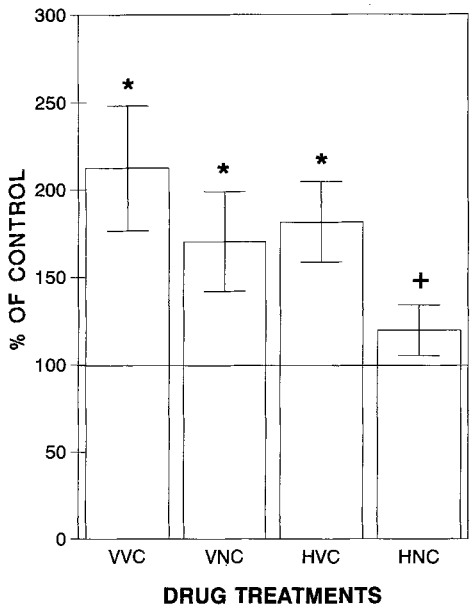

Fig. 1. The effects of vehicle (*V*) or haloperidol (*H*, 0.05 mg/kg) and vehicle or nimodipine (*N*, 10 mg/kg) on locomotor activity induced by cocaine (*C*, 10 mg/kg) as measured by counting interruptions of photobeams transecting the test cages. Neither haloperidol nor nimodipine significantly decreased cocaine's effects, but the two drugs in combination blocked locomotor activity produced by cocaine. *Significantly different from controls, $P < 0.05$, multiple F test. $^{+}$Significantly different from VVC, but not from controls, $P < 0.05$, multiple F test

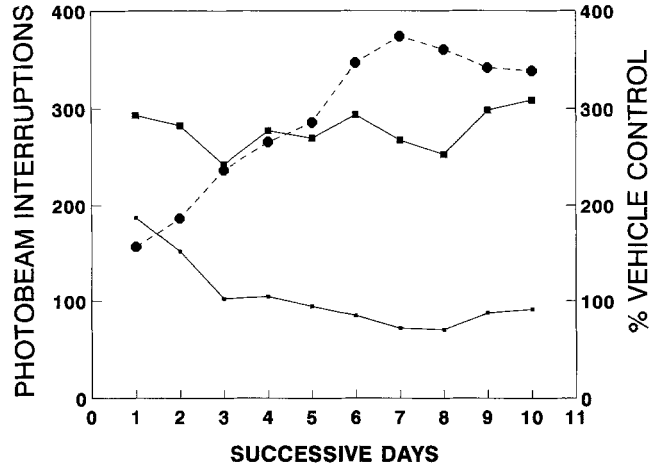

Fig. 2. The effect of cocaine injections (10 mg/kg, IP, $n = 48$) over 10 consecutive days as a percent of vehicle controls (*circles* and *dotted lines*, right axis) or as raw data (*boxes with solid lines*, left axis). The cocaine group differed significantly from the vehicle controls on each day (planned comparisons, multiple F test, $P < 0.05$), and the difference between the two groups increased over days

(Fig. 3). ANOVA indicated that there were significant main effects of previous treatment with cocaine [$F(1,88) = 22.26$, $P < 0.001$] and of present treatment with nimodipine [$F(1,88) = 15.1$, $P < 0.001$]. ANOVA indicated that only cocaine treatment had a significant effect over the 3 days of retraining [$F(1,88) = 88.0$,

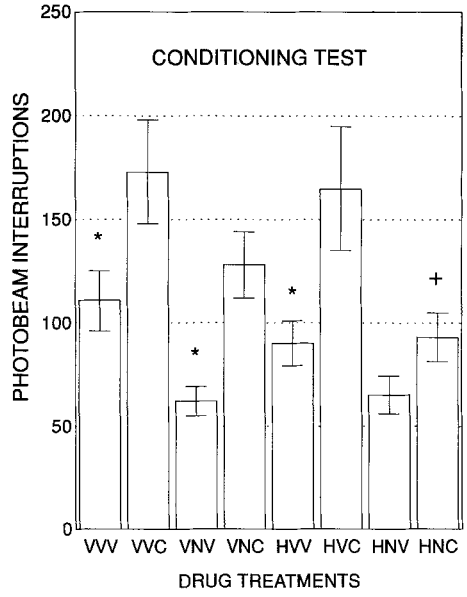

Fig. 3. The effect of treatment with vehicle (*V*), haloperidol (*H*, 0.05 mg/kg, IP) or nimodipine (*N*, 10 mg/kg, SC) on the expression of conditioned locomotion as measured by counting photobeam interruptions (mean counts ± SEM) in an environment previously associated with cocaine treatments, but tested in the absence of cocaine treatment on this day. The final V or C in each three-letter drug code designation refers to previous treatment history. For example, HNC refers to a group that received haloperidol and nimodipine injections 70 min prior to a vehicle injection, after which testing began, but this group had previously received ten consecutive daily cocaine-context pairings. Note that neither nimodipine nor haloperidol alone (*VNC* and *HVC*) reduced conditioned locomotion relative to the appropriate control groups (*VNV* and *HVV*, respectively), but the combination of the two drugs (*HNC*) did. * Significant difference between groups that received vehicle during conditioning and the comparable groups that were conditioned with cocaine, $P < 0.05$, multiple F test. $^{+}$ Significantly different from VVC group, $P < 0.05$, multiple F test

$P < 0.001$; data not shown]. In the sensitization test, the main effects of cocaine and nimodipine were also significant, but as can be seen in Fig. 4, nimodipine by itself was sufficient to attenuate cocaine-induced sensitization [Main effect of cocaine: $F(1,88) = 18.8$, $P < 0.001$; Main effect of nimodipine: $F(1,88) = 15.4$, $P < 0.001$].

Discussion

The major finding of this study is that nimodipine, an L-type calcium channel antagonist, blocked the expression of sensitization to cocaine, but not the expression of the classical conditioning of cocaine's locomotor effects. Haloperidol, a relatively selective antagonist for dopamine D_2 receptors, was without effect on either the sensitization or the classical conditioning of cocaine's locomotor effects. However, the combination of nimodipine and haloperidol blocked the expression of the classical conditioning of cocaine's motor stimulant effects, similar to the results in the acute study investigating direct effects on cocaine-induced locomotion. In the acute study, neither nimodipine nor haloperidol was sufficient to block

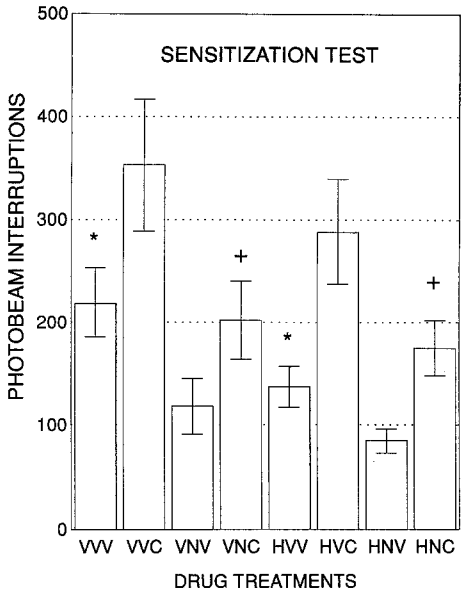

Fig. 4. The effect of treatment with vehicle (*V*), haloperidol (*H*, 0.05 mg/kg, IP) or nimodipine (*N*, 10 mg/kg, SC) on the expression of behavioural sensitization to cocaine as measured by counting photobeam interruptions (mean counts ± SEM). The final V or C in each three-letter drug code designation refers to previous treatment history. For example, *HNV* refers to a group that received haloperidol and nimodipine injections 70 min before a cocaine (10 mg/kg, IP) injection, after which testing began, but this group has previously received ten consecutive daily vehicle-context pairings. Note that nimodipine (*VNC* and *HNC*) reduced cocaine sensitization relative to the appropriate control groups (*VNV* and *HNV*, respectively), but haloperidol was without additional effect. * Significant difference between groups that received vehicle during conditioning and the comparable groups that were conditioned with cocaine, $P \equiv 0.05$, multiple *F* test. $^{+}$ Significantly different from VVC group, $P < 0{,}05$, multiple *F* test

cocaine's motor stimulant effects, but the two drugs together did. However, the action of the combination treatment on cocaine sensitization was not appreciably different fro—m the effect of nimodipine alone. These data indicate that the expression of sensitization and classical conditioning of cocaine's locomotor effects can be pharmacologically dissociated, as was previously reported for the development of these phenomena (Reimer and Martin-Iverson 1993). It is therefore likely that there are at least some physiologically different processes underlying sensitization and classical conditioning to cocaine.

It was found in a previous study that nimodipine, but not haloperidol, blocked the development of classical conditioning to cocaine (Reimer and Martin-Iverson 1993), and that either nimodipine or haloperidol attenuated the development of sensitization to cocaine. Furthermore, it was found that neither nimodipine nor haloperidol blocked the establishment of classical conditioning of amphetamine's motor stimulant effects, but the combination treatment did (DiLullo and Martin-Iverson 1992b). The effects of these drugs on the expression of classical conditioning of cocaine are different from their effects on development of conditioning to cocaine but are similar to the development of conditioning to amphetamine: neither agent alone is effective at blocking expression, but the two antagonists given in combination do block expression of cocaine conditioning.

The effects of nimodipine and haloperidol on the expression of behavioural sensitization to cocaine are different from their effects on the development of sensitization to cocaine. Either of the antagonists attenuates the development, but only nimodipine blocks the expression of cocaine sensitization. This dissociation supports the view that the neural substrates of the expression of these effects are different in some ways from the substrates of their development (Beninger and Hahn 1983; Beninger and Herz 1986).

There has been some debate as to whether context-specific stimulant-like effects and context-specific sensitization are due to classic conditioning, or to some other process such as enhancement of the activation properties of novel stimuli (Gold et al. 1988), blockade of habituation or "behavioural reorganization" (Damianopoulos and Carey 1992). Doubt of the applicability of Pavlovian conditioning to the observed phenomenon has arisen because the development of sensitization to cocaine is often only in relation to progressive decreases in the motor activity of the control group (i.e. chiefly due to habituation in the control group, rather than increases in the drug group). Furthermore, the level of context-elicited locomotion in the drug group on the drug-free conditioning test is often similar to the level of locomotion in the control group on the first day of testing. These characteristics are features in the present results. Figure 2 indicates that the level of locomotion induced by cocaine is relatively stable over the 10 days; sensitization is apparent only when expressed as a percent of control. In other experiments, the same dose of cocaine produces augmentation of the locomotor counts when continued over 14 days rather than ten (Burger and Martin-Iverson, in preparation). Sensitization is also clearly not related to habituation in the control group in the locomotor activity of animals treated with a D_2 agonist, PHNO (Martin-Iverson and McManus 1990). On the conditioning test, the experimental group in the present report exhibited higher levels of locomotion than the control group, but the level of locomotion was less than that produced by cocaine itself, and was similar to the level exhibited by the control group on the first day of testing, prior to habituation. However, it should be remembered that the conditioning test is also a day of extinction; the level of locomotion would therefore be expected to be less. In addition, the level of locomotion on the test day can be increased by restricting the temporal association of the cues with the peak effect of the stimulant during conditioning (Hiroi and White 1989). Finally, the choice of the behavioural measure determines whether or not processes other than Pavlovian conditioning is involved. Recent data from this laboratory have indicated that neither locomotion nor rearing behaviour exhibit patterns that can be confidently ascribed to classical conditioning, but other behaviours such as sniffing, head movements, and snout contact with a cage surface do appear to be classically conditioned to contextual stimuli (Martin-Iverson and DiLullo, in preparation). Classical conditioning is probably one of a variety of processes that underlie context-specific locomotion.

Interest has been growing in the conditioning of effects of stimulants in humans as a contributing factor to drug "craving" (O'Brien et al. 1988). DiLullo and Martin-Iverson (1992b) suggested that a combination treatment of nimodipine and haloperidol may be effective in attenuating this craving on the basis of the effects of the combination therapy on blocking the development of conditioning to amphetamine. However, the efficacy of nimodipine alone in blocking cocaine conditioning (Reimer and Martin-Iverson 1993) may indicate that the addition of haloperidol is not necessary for blocking craving. The ability of another L-type calcium channel antagonist to block the development of place preferences induced by cocaine supports this suggestion (Pani et al. 1991). The present results indicate that the combination therapy is likely to be necessary to block craving induced by conditioned stimuli, since it is the expression of this conditioning that would require blockade in cocaine abusers.

Certain investigators (e.g. Angrist 1983; Robinson and Becker 1986) have suggested that behavioural sensitization to psychomotor stimulants provides an animal model of stimulant psychosis, and possibly schizophrenic psychosis. If this model has construct validity then the present results suggest that nimodipine may be an effective treatment for psychoses, since it can be attenuate both the development and expression of sensitization to cocaine. Nimodipine could be an efficacious therapy or adjunct therapy for schizophrenia, since the L-type calcium channel blockers are relatively innocuous with respect to side-effects. Indeed, it has been suggested that drugs of this class can alleviate tardive dyskinesia (Bartko et al. 1991). Furthermore, serum calcium levels appear to increase during psyhotic episodes (Carman and Wyatt 1979), and preliminary uncontrolled studies have indicated a possible utility of L-type calcium channel antagonists as an adjunct therapy to neuroleptics for the alleviation of schizophrenic symptoms (Lapierre 1978; Bartko et al. 1991), although this has been questioned (Silverstone and Grahame-Smith 1991).

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