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Nimodipine and haloperidol attenuate behavioural sensitization to cocaine but only nimodipine blocks the establishment of conditioned locomotion induced by cocaine

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Abstract. The classical conditioning of the behavioural effects of cocaine has been shown to contribute to behavioural sensitization. In the present experiments, it was demonstrated that the effects of cocaine in rats can be conditioned to contextual stimuli. Furthermore, sensitization to cocaine's locomotor effects were demonstrated, and shown to be context specific. Nimodipine (10 mg/kg, SC), an L-type dihydropyridine Ca^{2+} channel antagonist, appeared to completely block the establishment of conditioning of cocaine's effects, but only partially blocked sensitization to cocaine. Haloperidol (0.05 mg/kg, IP), a relatively specific D_2 dopamine receptor antagonist, attenuated behavioral sensitization but had no influence on the establishment of the conditioned component of cocaine. These results indicate that the sensitization to, and the development of classical conditioning of, cocaine's behavioural effects can be pharmacologically dissociated, but that a non-associative process involved in sensitization is normally overridden by conditioning factors.

Key words: Cocaine – Nimodipine – Haloperidol – L-type Ca^{2+} channels – Behavioral sensitization – Classical conditioning – 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 (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; Baldo and Kelley 1991; Stewart and Vezina 1991). Sensitization to amphetamine is a function of at least two independent processes; a non-associative process, and an associative process (Robinson and Becker 1986). For example, behavioral sensitization occurs at night in rats that receive continuous infusions of amphetamine or a direct dopamine agonist using osmotic minipumps while the rats remain in their home cages (Martin-Iverson et al. 1988a,b; Martin-Iverson 1991). Stewart and Vezina (1991) found that amphetamine-induced sensitization of locomotion and rearing were exclusively context dependent. However, following extinction of conditioning, context-independent sensitization emerged for locomotion but not rearing. These results are important in that they show that a) sensitization can occur to amphetamine without context specificity at least for certain behaviours, and b) that the effects of classical conditioning overrides the influence of the non-associative component.

The establishment of classical conditioning of the locomotor effects of amphetamine and cocaine has been shown to be blocked by pimozide (Beninger and Hahn

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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 classical conditioning of amphetamine's effects appears to be dependent upon two separate processes, one which is neuroleptic sensitive and one which involves the impulse-dependent L-type calcium channels. Other work (DiLullo and Martin-Iverson 1991, 1992a) has shown that the conditioning of amphetamine's locomotor effects does indeed involve two separate processes: Ca^{2+}-dependent release of dopamine from vesicles (reserpine sensitive), and Ca^{2+}-independent release from a newly synthesized dopamine compartment (sensitive to synthesis inhibition by alpha-methylparatyrosine). However, the mechanisms underlying the conditioning of cocaine have not been clarified to the same extent.

The purposes of the present experiments were to establish dose-response relationships for the classical conditioning of cocaine's locomotor effects and the development of locomotor sensitization to cocaine, and to determine the role of Ca^{2+} channels and D_2 receptors in the development of these two processes. Rats received cocaine injections prior to confinement in a unique environment or in their home cages as a pseudo-conditioned control for context-independent effects. The effects of haloperidol, a dopamine antagonist relatively selective for D_2-like receptors, and nimodipine, an L-type calcium channel blocker, on the establishment of cocaine conditioning and sensitization were also investigated. These two drugs were chosen because they have previously been shown to block the conditioning of amphetamine's locomotor effects when given in combination but not when given alone (DiLullo and Martin-Iverson 1992b).

Materials and methods

Animals. In both experiments, experimentally naive male Sprague-Dawley rats weighing between 250 and 350 g were purchased from the Health Sciences Animal Services of the University of Alberta. All rats were housed in pairs in a climatically controlled room (20–22°, humidity = 50%). They were on a 12-h light-dark cycle (0700 to 1900 hours) with free access to food and water. All procedures used were approved by the Health Sciences Animal Care Committee as following CCAC recommendations for animal use in research.

Equipment. The locomotor activity test boxes measured 25 cm (H) × 25 (W) × 30 (L) and contained two infrared photocell assemblies placed 3 cm from the floor and 14 cm apart, equidistant from the end walls. The sensitivity of the photocells was adjusted such that only gross movements were counted. Fine repetitive movements of the head, tail, and paws were excluded.

Procedures. Rats in all groups were habituated to their home cages for 7 days prior to the experiment. Both experiments included daily injections of cocaine for 10 consecutive days with a 60-min measurement of locomotor activity on each of these days, followed by 3 days in which the rats were left in their home cages, with a test given on day 14 when all animals received vehicle injections prior to locomotor testing for 60 min. Half of the rats received the drugs paired with the test boxes (Paired), and the other half received the drugs 2 h after removal from the test boxes while the animals were in their home cages (Unpaired). The latter groups served as the "pseudo-conditioning controls". In the first experiment, the test day was followed by an additional test on day 15, in which all animals received a challenge dose of cocaine-HCl (10 mg/kg, IP) prior to measurement of locomotor activity.

Groups of rats in experiment 1 were given cocaine [0 (vehicle), 5, 10, or 20 mg/kg, IP], with 12 rats per group for a total of 96 animals. The drug groups in experiment 2 were VVV, VVC, VNV, VNC, HVV, HVC, HNV, and HNC where V = vehicle, H = haloperidol, N = nimodipine, C = cocaine. Each group included 12 animals for a total of 192 rats. Nimodipine (10 mg/kg, SC) and haloperidol (0.05 mg/kg, IP) were injected 70 min prior to cocaine (10 mg/kg, IP), and cocaine was injected just prior to placement of the animals in locomotor activity measuring boxes or 2 h after removal from the test boxes, while the rats were back in their home cages.

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 5, 10, or 20 mg/ml solutions using double-distilled water.

Statistics. The raw locomotor counts from each group were expressed as percent of the mean of the vehicle control for that group. The data were subjected to analysis of variance (ANOVA). Experiment 1 had two independent factors: Context (2 levels: Paired or Unpaired) and Cocaine dose [4 levels: 0 (vehicle), 5, 10, or 20 mg/kg]. There was also a repeated factor for the conditioning phase of the experiment (Days with 10 levels). In experiment 2, there were four independent factors: Context (2 levels: Paired or Unpaired), Cocaine (2 levels: 0 or 10 mg/kg), Haloperidol (2 levels: 0 or 0.05 mg/kg), and Nimodipine (2 levels: 0 or 10 mg/kg). There was also a repeated factor for the conditioning phase, Days (10 levels). Since ANOVA with more than two repeated measures is unreliable due to lack of homogeneity of covariances (Vitaliano 1982), a variety of multivariate tests of significance (Pillais Trace, Hotellings T, Wilks Lambda, and Roys F-test) were also conducted for terms involving this factor, as is standard procedure with the statistical software used (Statistical Package for the Social Sciences). 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

Experiment 1

Statistical analyses were conducted separately for the three phases of this experiment: the 10 days of condition-

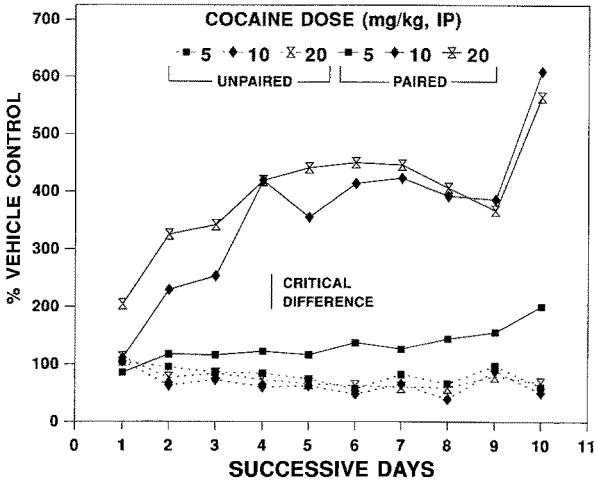

Fig. 1. Motor stimulant effects of daily injections of cocaine at the indicated doses, as a percent of the locomotion of the respective vehicle groups. Injections were given to rats either immediately preceding locomotor testing (*PAIRED*) or 2 h after removal from the test boxes (*UNPAIRED*). The *line* representing the critical difference required for differences in the means to be significant with alpha = 0.05 is derived from the Multiple *F* procedure for individual comparisons. Note that the groups receiving 10 and 20 mg/kg cocaine paired with the test boxes exhibit equivalent degrees of sensitization, and that even the lowest dose, which has no effect initially, develops some significant stimulant effects by day 10

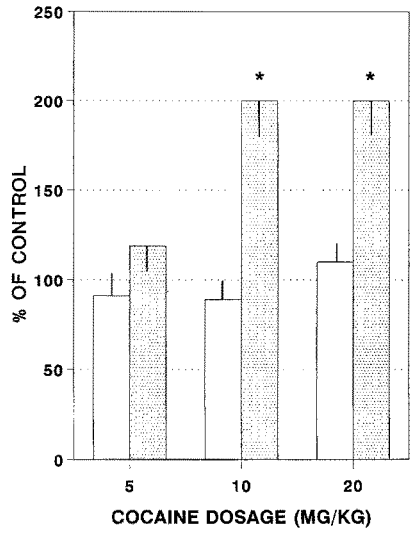

Fig. 2. Motor stimulant effects conditioned to the test context by prior daily injections of cocaine at the indicated doses paired (▨) or unpaired (□) with the test context, as a percent of the locomotion of the respective vehicle groups (data in text). *Bars* represent the SEM of each group. On this test, all rats were given vehicle injections only. The groups given previous injections of 10 or 20 mg/kg cocaine paired with the test context exhibited increases in locomotion relative to vehicle groups. * Significantly different from the paired vehicle injected group, $P < 0.05$

ing, the drug-free test day (day 14) after the 3-day washout period and the cocaine challenge day (day 15). There were no significant differences in the photobeam interruptions (locomotion) between the paired and unpaired groups treated with vehicle (data not shown) during conditioning. As can be seen in Fig. 1, the 10 and 20 mg/kg doses of cocaine increased locomotion, and this effect exhibited a gradual augmentation over the days of treatment (behavioral sensitization). The lowest dose (5 mg/kg) given to the paired groups did not produce much locomotion nor did much evidence of sensitization emerge, except for a significant increase in locomotion on day 10. ANOVA revealed a significant Context by Dose by Days interaction [$F(27,792) = 4.25$, $P < 0.001$] for the conditioning phase of the experiment. On the drug-free test for conditioned locomotion on day 14, ANOVA indicated that there was a significant Context by Dose interaction [$F(3,88) = 6.78$, $P < 0.001$]. Paired groups previously treated with 10 or 20 mg/kg cocaine exhibited significantly higher levels of locomotion than did controls (Fig. 2). The group of rats given 5 mg/kg cocaine paired with the testing context, and all of the unpaired controls did not exhibit increased locomotion. There was no significant difference in photobeam interruptions between the paired and unpaired vehicle groups on day 14 (unpaired mean = 209, SEM = 14.6; paired mean = 188.8, SEM = 21.9). ANOVA also indicated that there was a significant Context by Dose interaction [$F(3,88) = 2.72$, $P < 0.05$] for the locomotor activity induced by the cocaine challenge on day 15. The test group that received 10 mg/kg cocaine paired with the test context during conditioning had the most robust sensitization in response to a challenge dose of cocaine on day 15 (Fig. 3). The group

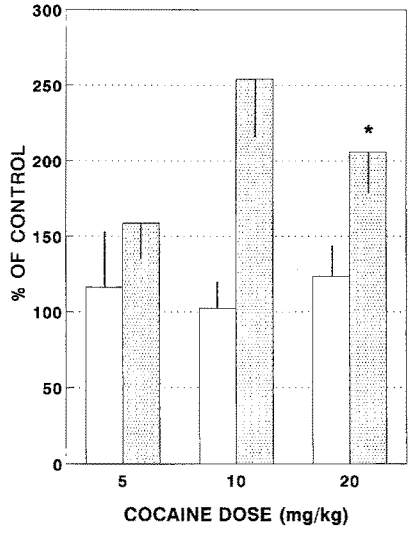

Fig. 3. Motor stimulant effects of a single treatment with cocaine (10 mg/kg, IP) given to rats with a prior history of cocaine treatments at the indicated doses paired (▨) or unpaired (□) with the test context, as a percent of the locomotion of the respective vehicle groups after a similar cocaine injection (data in text). *Bars* represent the SEM of each group. Only the groups given previous injections of 10 or 20 mg/kg cocaine paired with the test context exhibited sensitization. * Significantly different from the paired chronic vehicle, acute cocaine (10 mg/kg) injected group, $P < 0.05$

receiving 5 mg/kg during conditioning and the unpaired drug groups did not exhibit sensitization to the 10 mg/kg challenge dose of cocaine. There were no significant differences in photobeam interruptions between vehicle groups after the cocaine challenge on day 15 (unpaired

mean = 346.2, SEM = 87.2; paired mean = 200.8, SEM = 38.8). These results demonstrate that cocaine sensitization was context dependent, i.e. it was absent in the cocaine-treated unpaired groups.

Experiment 2

In this experiment, statistical analysis was conducted separately for the 10 days of conditioning (and drug treatments) and the drug-free test day. All groups showed a relatively high level of locomotor activity on day 1 which decreased substantially thereafter (habituation). No significant differences were observed in the locomotor activity among the groups that received vehicle or haloperidol, vehicle or nimodipine and vehicle control groups (i.e. VVV, HVV, VNV, HNV) either with injections unpaired with the test boxes or with injections paired with exposure to the test boxes during conditioning. Groups receiving cocaine 2 h after removal from the test boxes (unpaired) did not exhibit locomotor activity in the test boxes 22 h after cocaine treatments different from their respective vehicle controls (Fig. 4). On the other hand, rats receiving cocaine paired with the test boxes exhibited levels of locomotion between 115 and 210% of controls on day 1, and between 275 and 480% by day 10 (Fig. 5). These data demonstrate the development of context-specific cocaine-induced behavioral sensitization to 10 mg/kg cocaine in the absence of changes in levels of spontaneous locomotion. This sensitization was attenuated (but not blocked) similarly by nimodipine and haloperidol. When the two antagonists were both given to the rats, the degree of attenuation was decreased. The validity of these observations are supported by a significant Context by Haloperidol by Nimodipine by Cocaine by Days interaction in the locomotor behaviour during con-

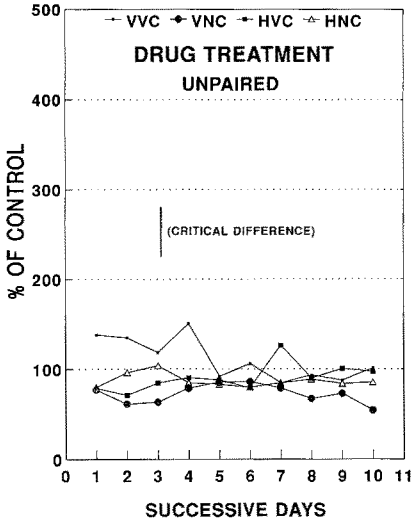

Fig. 4. Motor stimulant effects over 10 days of vehicle (*V*), 0.05 mg/kg haloperidol (*H*), 10 mg/kg nimodipine (*N*) and 10 mg/kg cocaine (*C*) unpaired with the test context (i.e. injections beginning 2 h after locomotor testing), as a percent of the respective vehicle injections (i.e. those treated with VVV, VNV, HVV or HNV). For example, the data from the VVC (vehicle + vehicle + cocaine) group are expressed as a percent of the mean from the VVV group, and those from the HNC (haloperidol + nimodipine + cocaine) group are expressed as a percent of the mean of the HNV group. Note that there are no significant differences among the groups. The critical difference line was obtained using the Multiple *F* test for individual differences

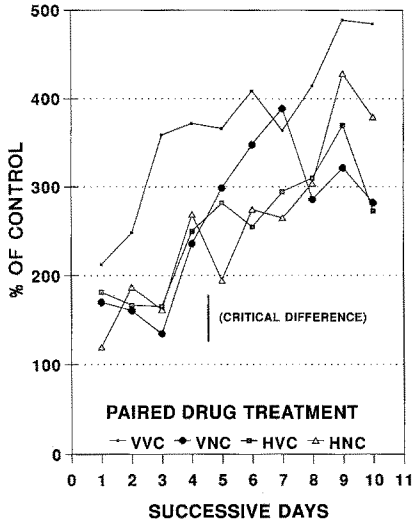

Fig. 5. Motor stimulant effects over 10 days of vehicle (*V*), 10 mg/kg nimodipine (*N*), 0.05 mg/kg haloperidol (*H*) and 10 mg/kg cocaine (*C*) paired with the test context, as a percent of the respective vehicle injections (i.e. VVV, VNV, HVV and HNV). For example, the data from the VVC (vehicle + vehicle + cocaine) group are expressed as a percent of the mean from the VVV group, and those from the HNC (haloperidol + nimodipine + cocaine) group are expressed as a percent of the mean of the HNV group. Note that all groups develop some degree of sensitization (i.e. locomotor stimulant effects of cocaine are augmented over days of treatment), but that co-treatment with either haloperidol or nimodipine attenuate sensitization. The critical difference line was obtained using the Multiple *F* test for individual differences

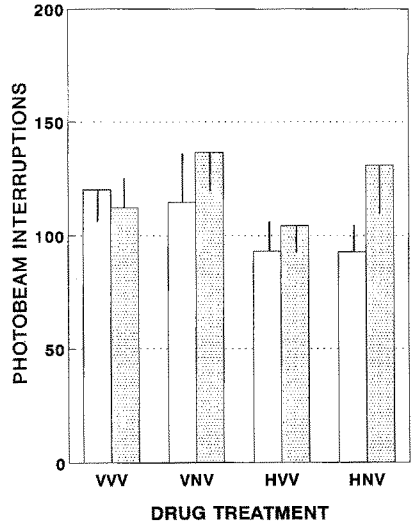

Fig. 6. Motor stimulant effects (mean number of photobeam interruptions ± SEM) conditioned to the test context by prior daily injections of vehicle (*V*), or 0.05 mg/kg haloperidol(*H*), 10 mg/kg nimodipine (*N*) or V, and V paired (▨) or unpaired (□) with the test context. On this test, all rats were given vehicle injections only. Note that there were no significant differences among the groups

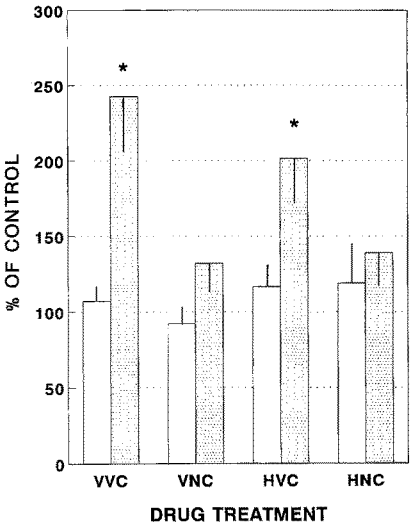

Fig. 7. Motor stimulant effects (% of appropriate vehicle controls as shown in Fig. 6, ± SEM) conditioned to the test context by prior daily injections of vehicle (*V*), or 0.05 mg/kg haloperidol(*H*), 10 mg/kg nimodipine (*N*) or V, and 10 mg/kg cocaine paired (▨) or unpaired (□) with the test context. On this test, all rats were given vehicle injections only. Note that only nimodipine blocked the conditioned locomotion produced by cocaine. * Significantly different from the appropriate control group, and from the unpaired group with the same drug treatment, $P<0.05$

ditioning [$F(9,1584)=2.19$, $P<0.025$]. On the drug-free day 14 testing for the presence of conditioned locomotion, ANOVA demonstrated a significant Context by Nimodipine by Cocaine interaction [$F(1,176)=4.35$, $P<0.038$]. Pretreatment of rats with haloperidol during the establishment of conditioning was without significant effects on the drug-free test of conditioned locomotion. There were no significant differences between pairs of the appropriate vehicle controls (Fig. 6). Context-specific cocaine conditioning was elicited and this conditioning was completely blocked by previous treatments during conditioning with nimodipine and by the combination of nimodipine and haloperidol but not by pretreatment during conditioning with haloperidol alone (Fig. 7).

Discussion

The present results indicate that when repeated daily injections of cocaine (5–20 mg/kg, IP) to rats are paired with a unique environment, the locomotor stimulant effects are gradually augmented over 10 days (behavioural sensitization), as has been previously reported (Barr et al. 1983; Beninger and Herz 1986). Sensitization was not apparent in rats that had received similar cocaine treatments in a context different from the locomotor testing when challenged with cocaine in the test context. Accompanying context-specific sensitization was the classical conditioning of the locomotor stimulant effects of cocaine to contextual stimuli. Only the groups that displayed a significant conditioned effect also exhibited sensitization after a challenge dose of 10 mg/kg cocaine. Sensitization to cocaine has previously been found to be context specific (Post et al. 1981; Weiss et al. 1989).

Although behavioural sensitization to cocaine appeared to be completely due to classical conditioning when rats were treated only with cocaine, these two phenomena could be dissociated from each other by additional pharmacological treatments. Haloperidol, a relatively selective antagonist for dopamine D_2 receptors, attenuated sensitization without influencing classical conditioning. The ability of haloperidol to decrease sensitization to cocaine (Weiss et al. 1989) and apomorphine (Mattingly and Rowlett 1989) has been published previously. Failure of haloperidol to block the establishment of amphetamine-conditioned locomotion has also been reported (Martin-Iverson and McManus 1990; DiLullo and Martin-Iverson 1992b). Nimodipine only partially blocked the development of sensitization, but completely blocked classical conditioning of cocaine's locomotor effects to contextual stimuli. This suggests that the previously found blockade of the establishment of cocaine-conditioned locomotion by pimozide (Beninger and Herz 1986) was due to the L-type calcium channel blocking actions of pimozide, not to its ability to antagonize dopamine D_2 receptors. The present results provide evidence that sensitization and conditioning to cocaine can be dissociated.

This "double-dissociation" rules out explanations of the effects due to differential sensitivity of the conditioning and sensitization test procedures to blockade. The test for the presence of conditioning is probably more susceptible to blockade than is the test for sensitization because of the absence of drug-related cues (possibly peripheral effects such as increases in heart rate), and the fact that the conditioning test occurs during extinction, while sensitization is tested during an additional training trial.

The most parsimonious explanation therefore appears to be that behavioural sensitization and conditioning can develop from separable processes. Sensitization appears to be controlled by conditioning factors, but a non-associative sensitization process is also present, and can be unmasked under special circumstances. One cautionary note concerning this conclusion should be observed: the effects of nimodipine and haloperidol at attenuating sensitization were not additive, as would be expected if the drugs acted by blocking independent processes.

In the present paper, sensitization was found to be context specific, but it could be doubly dissociated from classical conditioning by haloperidol, which attenuates sensitization without influencing conditioning, and nimodipine, which completely blocks conditioning but only partially attenuates sensitization. A similar dissociation between sensitization and conditioning has been reported for amphetamine, using behavioural procedures (Stewart and Vezina 1991). Amphetamine-induced sensitization of locomotion and rearing were found to be completely context dependent. However, if the conditioning component underwent extinction over a number of trials, a degree of context independent sensitization emerged for locomotion but not for rearing. Thus, at least one type of behavior exhibited some degree of non-associative sensi-

tization when classical conditioning was extinguished. Stewart and Vezina suggested that the masking of the relatively weak non-associative sensitization by classical conditioning could have occurred by the association of the testing context of the pseudo-conditioned control groups with the absence of drug, making the test context an S– for (in their case) amphetamine. After extinction, the S– properties of the test context would be extinguished, and the non-associative sensitization emerges. In this way, classical conditioning procedures come to control the development and expression of sensitization to stimulants, overriding a non-associative component.

It has been clearly shown that continuous administration of amphetamine (Martin-Iverson 1991; Nielsen 1981), cocaine (Post et al. 1981) and a direct agonist for the D_2 dopamine receptor, (+)-4-propyl-9-hydroxynaphthoxazine (PHNO, Martin-Iverson et al. 1987, 1988a,b; Martin-Iverson 1991) result in behavioural tolerance during the day. Thus, a treatment regimen that does not allow specific contextual stimuli to become associated with the drug effect does not appear to produce sensitization. The same treatment regimens that produce behavioural tolerance during the day also result in sensitization at night (Martin-Iverson et al. 1987, 1988a,b; Martin-Iverson 1991). These effects cannot be explained by associative processes, and are due to circadian rhythms since the pattern of tolerance/sensitization follows the free-running rhythms in motor activity under conditions of constant lighting (Martin-Iverson and Yamada 1992). However, recent work from our laboratory has shown that the same is not true for cocaine: tolerance occurs to cocaine-induced behaviours during both day and night (Burger and Martin-Iverson, in preparation).

There appear to be fundamental differences in the sensitization to, and conditioning of, cocaine's motor stimulant effects relative to those of amphetamine and PHNO. Besides the differences in nocturnal sensitization just noted, neither haloperidol nor nimodipine block the establishment of conditioning of amphetamine's locomotor effects, but the two drugs given together can block this conditioning (Martin-Iverson and McManus 1990; DiLullo and Martin-Iverson 1992b). Haloperidol was found to be ineffective at attenuating sensitization to a direct and selective agonist for DA D_2 receptors (Martin-Iverson and McManus 1990). Therefore, it appears that neither stimulant-induced sensitization nor classical conditioning of stimulant effects are functions of single common mechanisms, but can occur by a variety of mechanisms, differing with the stimulants and treatment regimens used.

Previous work has shown that the conditioning of amphetamine's behavioural effects involves two independent processes, a Ca^{2+}-dependent and a Ca^{2+}-independent mechanism, each of which can support conditioning in the absence of the other (DiLullo and Martin-Iverson 1992a,b). The present finding that an L-type calcium channel antagonist (nimodipine) can block the conditioning of cocaine's motor effects indicates that the conditioning of cocaine occurs via a single Ca^{2+}-dependent mechanism.

Other research supports a role for L-type Ca^{2+} channels in cocaine-induced effects. For example, nitrendipine blocks the cardiac toxicity and lethal effects of cocaine (Trouve and Nahas 1986). Isradipine inhibits a cocaine-conditioned place preference (Pani et al. 1991b) and isradipine and nimodipine prevent cocaine-induced dopamine release and motor activity in rats (Pani et al. 1991a). Taken together with the present results, these data indicate that nimodipine may be effective as a treatment for cocaine addiction and for cocaine-induced psychoses.

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