Pharmacology Biochemistry and Behavior, Vol. 60, No. 4, pp. 847–853, 1998

0091-3057/98 $19.00 + .00

ELSEVIER

PII S0091-3057(98)00063-X

A Combination of Isradipine and Naltrexone Blocks Cocaine's Enhancement of a Cocaine Place Preference

CHRISTOPHER M. CRAMER, CHRISTOPHER L. HUBBELL AND LARRY D. REID

Laboratory for Psychopharmacology, Rensselaer Polytechnic Institute, Troy, NY 12180

Received 11 July 1997; Revised 2 December 1997; Accepted 8 February 1998

CRAMER, C. M., C. L. HUBBELL AND L. D. REID. *A combination of isradipine and naltrexone blocks cocaine's enhancement of a cocaine place preference.* PHARMACOL BIOCHEM BEHAV **60**(4) 847–853, 1998.—Rats were conditioned by pairing cocaine with one side of an alley and placebo with the other. After conditioning, compared to Baseline and a placebo-control group, rats spent more time in the place of cocaine experience. Subsequently, there were further tests except now cocaine was given just before the test session in addition to one of two other kinds of injections. One of these additional injections was a placebo and the other was a combination of a small dose of isradipine (1 mg/kg) and a dose of naltrexone (3 mg/kg) (ISR+NTX). Measures of gross activity (movement from one side of the alley to the other) were taken during testing. ISR+NTX blocked cocaine's ability to sustain a place preference. ISR+NTX also blocked sensitization of cocaine's ability to enhance locomotor activity. This blockade of cocaine's usual effects indicates that ISR+NTX may have a role in treating cocaine use disorders. © 1998 Elsevier Science Inc.

Cocaine Isradipine Naltrexone Conditioned place preference Addiction

ISRADIPINE (ISR) is a calcium channel inhibitor useful in treating hypertension (8). Naltrexone (NTX) is an opioid antagonist useful in treating heroin and alcohol use disorders [for reviews, see (16,20)]. There is evidence to suggest that both ISR and NTX might attenuate the reinforcing properties of cocaine (3,10,13,14,17–19,21,24,25). Perhaps, small doses of ISR combined with doses of NTX might be an effective intervention in the treatment of cocaine use disorders. There are reasons to be interested in small doses of the two in combination, because of the possibility that the two might have additive effects in terms of addiction-relevant effects, but not in terms of side effects that might interfere with compliance to take the combination.

It has recently been shown that a combination of ISR, 1.0 mg/kg, and NTX, 3.0 mg/kg (ISR+NTX), blocks cocaine's ability to enhance pressing for rewarding brain stimulation (24). Neither the dose of ISR nor of NTX are sufficiently large by themselves to block cocaine's effects [(14,25); unpublished data]. When no cocaine is given, moderate doses of ISR+NTX (larger than those used in the combination) do not significantly reduce pressing for brain stimulation. These effects support the conclusion that ISR+NTX would block effects relevant to cocaine use disorders without producing problematic side effects.

The conditioned place preference (CPP) procedure was designed to assess, among rodents, the affect induced by drugs (26,29). Basically, the procedure involves having an alley with at least two distinct places. These two places can be separated by a removable barrier. After measuring a baseline preference for being in each place without the barrier, the effects of a test drug are paired with one of the places. The pairing usually involves merely confining a rat under the influence of the test drug in one place. Subsequently, under the influence of a placebo, the rat is confined in the other place. After pairing the test drug's effects with one place and the placebo's effects with another place, a test is done. A test involves placing the rat in the alley without a barrier (as during Baseline) and measuring the time spent in the place of drug experience. The test is usually done with the rat receiving no injections. When the pharmacodynamic effects of drugs having high addiction

Requests for reprints should be addressed to L. D. Reid, 302 Carnegie Hall, Laboratory for Psychopharmacology, Rensselaer Polytechnic Institute, Troy, NY 12180-3590.

liability are paired with a place, rats subsequently, on average, spend more time in that place than they did at baseline and more time than a comparable group treated with only placebos, i.e., they establish a CPP (7,27).

Instead of doing the test for a CPP without an injection, Bozarth (6) injected the drug just before a test. The injection resulted in a larger preference for the place of the previous experience of the drug. It is as if the effects of the drug at testing strengthened the effects of conditioning. We (10) have recently shown that cocaine, when given during testing, enhanced a cocaine CPP.

Experiment 1

A recent study indicates that ISR+NTX also blocks the establishment of a cocaine CPP (10). Because dosing with ISR+NTX began 30 days before the CPP procedures, the study also indicates that the combination's effects did not wane or show tolerance with repeated dosing.

The procedures of this experiment were designed to ask whether ISR+NTX would block cocaine's ability to enhance an established cocaine CPP. We believe that knowledge from such a test is particularly relevant to treating patients' cocaine use disorders. Persons trying to abstain from using cocaine often succumb to using cocaine again while vowing to never again engage heavy use of the drug. However, with the experience of initial dosing, there is a marked tendency to reinstate the behaviors of heavy drug use. A useful adjunct to other treatments for cocaine use disorder is apt to be a drug that would block the full relapse back into heavy cocaine use when some cocaine or cocaine-like effects are experienced. On the surface, it seems that a drug that would block cocaine's ability to enhance an already established cocaine CPP among rats, would also be effective in curbing binge use of cocaine and would prevent a full relapse back into heavy use of cocaine by people trying to achieve extended abstinence.

METHOD

Subjects

Forty-eight rats were purchased from Taconic Farms (Germantown, NY) when they weighed about 200 g. They were housed in individual hanging cages where they always had food and water. The windowless room housing the rats was maintained at 22 ± 2°C and had 12 h of incandescent light daily beginning at 0700 h.

Drugs and Injections

The dose of cocaine HCl (from Sigma) was 5 mg/kg. The combination, ISR+NTX, was 1 mg/kg of ISR (from Novartis) plus 3 mg/kg of NTX HCl (from DuPont-Merck). All injections were 1 ml/kg, given intraperitoneally.

The carrier of cocaine was physiological saline (0.9% NaCl). The carrier of the other agents was a solution of 5% Tween 80 (polyoxyethylenesorbitan monooleate) in physiological saline. Placebos associated with cocaine and the combination were injections of their respective carriers.

Apparatus

The apparatus is 12 nearly identical alleys, and is described in detail elsewhere (23). The two halves have distinct visual and textural cues. The walls of one-half were painted gray, while the walls of the other half were painted with black and white horizontal stripes. Steel rods forming the floor of the alley are perpendicular to the length of the alley in the gray side and horizontal in the other side. Two dividers were used, on different occasions, to separate the halves of the alley: one has a large hole (12 cm in diameter) allowing the rats free access to both sides, the other has no hole and was used to confine a rat to one side of the alley.

Each half of the alley has an adjustable light overhead. When the brightness of the sides of the alley are nearly the same, rats show no reliable preference for one side over the other. In these procedures, however, one side was made brighter than the other, which in turn, produced a preference, at baseline, for the darker half of the alley. For six of the alleys, the side with gray walls was the brighter place; and, for the other six, the side with striped walls was brighter. The effects of cocaine were paired with the brighter side of the alley.

During baseline and tests, when a rat moves from one side of the alley to the other, an electrical circuit is completed. Using these signals, a computer and the software developed for this system (23) automatically tabulated the time on each side of the alley and the number of times the rat crossed from one side of the alley to the other.

Procedure

The procedure involved daily sessions given in the following order: (a) habituation to the general procedures; (b) baseline measurement; (c) conditioning; (d) test 1, a test for a cocaine CPP; (e) tests 2, 3, and 4, which were tests for "cocaine enhancement" with and without ISR+NTX, and concurrently, tests for cocaine-induced activity; (f) test 5, a test following cocaine injections but without ISR+NTX; and (g) test 6, a test identical to baseline.

Before conditioning and across 3 days, all subjects were handled extensively to habituate them to the general procedures. As part of that handling, they were transported, by way of a mobile rack of cages, to the room of the apparatus (the room of the apparatus was next to the room of the rat's home cages). On two consecutive occasions, each rat was placed in its assigned alley for 30 min with access to both sides of the alley. On the second of these occasions, the time spent on each side of the alley was measured. Based on the time spent in the brighter side of the alley (i.e., baseline), two groups of subjects ($n = 24$) were formed so that their mean baseline scores were nearly equal. One group was assigned to receive cocaine and the other saline during putative conditioning.

Conditioning involved using the barrier that confined a rat to only one side of the alley. A conditioning session was 30 min. Injections, either cocaine or saline, were given just before a rat was placed into a side of the alley. On the first day of conditioning, all rats received saline and were placed in the darker side of its alley. On the next day, the rats received their assigned injections of either saline or cocaine and placed in the brighter side of the alley, i.e., the side of putative conditioning. The procedures of the first 2 days of conditioning were repeated six times. Consequently, at the end of conditioning, half of the rats had received cocaine in the brighter side on six occasions and saline on the other side on six occasions. The other half had received only saline, but otherwise were handled as the half getting cocaine.

On the day after conditioning, there was a test (test 1) for the effects of conditioning. Each rat was placed into its alley with access to the entire alley for 30 min. No injections were given before test 1, i.e., the procedures were the same as those of baseline.

After test 1, the rats of the cocaine and saline groups were each subdivided into two groups ($n = 12$), such that the subgroups mean preference scores at test 1 were nearly equal. These subgroups were assigned to receive either ISR+NTX or its placebo across tests 2–4. The groups' labels, cocaine–placebo, cocaine–ISR+NTX, saline–placebo, and saline–ISR+NTX, refer to their conditioning injections (cocaine or saline) and their injections unique to tests 2–4 (ISR+NTX or placebo).

Tests 2–4 occurred on consecutive days beginning the day after test 1. Tests 2–4 were similar to test 1, except that all subjects received an injection of cocaine immediately before each test. Furthermore, the subjects also received their assigned injections of either ISR+NTX or placebo 30 min before testing.

Test 5 was identical to tests 2, 3, and 4, except that no injections associated with ISR+NTX were given. All rats received cocaine before test 5. Test 6 was identical in procedure to baseline, except of course, now the rats had differential histories.

Data Reduction and Statistics

For baseline and the tests, two kinds of scores are automatically tabulated: (a) proportion of time spent on the side of putative conditioning, the measure of CPP; and (b) number of times the rats crossed from one side of the box into the other, a rough measure of gross activity. Each kind of score was analyzed separately.

To answer the question of whether conditioning modified the rats' preference for the place of cocaine experience, the two groups of scores of proportions at baseline were compared to those of test 1 and to each other. These data conform to a 2 by 2 analyses of variance (ANOVA) for repeated measures having factors of (a) experiencing cocaine or placebo in the brighter side of the alley, and (b) baseline vs. test 1. Given that baseline scores were arranged to be similar across groups, and given the expectation that cocaine would enhance the proportion of time spent in the brighter side, the expected outcome of the ANOVA is a reliable interaction between the two factors. That was, indeed, the outcome of that ANOVA, the values for the interaction were $F(1, 46) = 6.7$, $p = 0.01$. The relevant analyses for confirming that cocaine produced a CPP, therefore, is an analyses for simple main effects at test 1.

An ANOVA of the data of proportion of time on side of putative conditioning of the two groups getting saline throughout conditioning indicates that these groups' scores did not differ reliably across the six tests of the procedures (mean across all saline subjects across all tests = 0.31). Given this consistency of scores of the saline–placebo and saline–ISR+NTX groups, their variability is not considered further in terms of CPP scores.

To answer the question of whether, within this experiment, an injection of cocaine can strengthen an established CPP, the revealing comparison is the scores of test 1 to those of test 2. The comparison of the scores of test 1 to test 2 of the cocaine–placebo group is indicative of whether cocaine enhanced a cocaine CPP. Further comparisons of that same group, however, of test 1 to tests 3 and 4 indicates that cocaine given before testing did not reliably enhance the CPP and the preference data associated with tests 3 and 4 are not discussed further. The reason for a diminishing enhancement effect is probably related to the fact that both placebo and cocaine effects were paired with both sides of the alley during tests 1 and 2, respectively, thereby, counterconditioning the effects of previous conditioning. Regardless of the explanation, it is apparent, given the fact that the enhancement effect is manifest only at test 2 in the cocaine–placebo group, that it is only during test 2 that we can assess whether ISR+NTX blocked the enhancement effect.

In summary, initial analyses showed that rats just getting saline do not reliably change their place preference across tests. Rats getting cocaine did change their preference (in comparison to their own baseline and in comparison to saline controls). These outcomes set the stage for the germane question: Does ISR+NTX reliably modify cocaine's enhancement of a cocaine CPP? Aid in answering that question is given by a between group *t*-test of the two groups conditioned with cocaine (placebo–controls and ISR+NTX) at test 2.

In addition to the preference scores, there are scores associated with movement from one side of the alley to another. During baseline, all subjects crossed from one side to another a mean of 25.4 times, whereas, during the test 1, all subjects made, on average 26.7 crosses. A 2 by 2 ANOVA of those data, with factors of cocaine vs. saline and baseline vs. test 1, failed to reveal any reliable sources of variance (all ps > 0.08) In brief, there was no reliable change in the mean number of crosses from baseline to test 1 for either the rats conditioned with cocaine or those that received only saline, a finding consistent with what we have observed before. Conditioning seems to affect proportion of time spent in a place somewhat independently of the number of times that subjects cross from one side to another. Given this circumstance, the activity scores during baseline and test 1 are not considered further.

Cocaine was given to all subjects before tests 2, 3, and 4. Half of the subjects had a history of cocaine injections associated with conditioning. Half the subjects also had ISR+NTX before tests 2, 3, and 4. The data of activity (number of crosses from one side of the alley to the other during the 30 min) conform to a 2 by 2 by 3 ANOVA, having repeated measures, with factors of history of cocaine injections (6 vs. 0 before test 2), ISR+NTX vs. placebo, and the three tests.

The results of test 5 conform to a 2 by 2 ANOVA with differential drug histories as the factors (10 vs. 4 doses of cocaine and 3 vs. 0 doses of ISR+NTX). The results of test 6 also conform to a 2 by 2 ANOVA with factors associated with differing drug histories.

RESULTS AND DISCUSSION

A one-way ANOVA of the data associated with preference scores for test 1, reveals that the two groups' mean scores were reliably different, $F(1,46) = 8.8$, $p = 0.005$: mean score of the saline group is 0.30, and mean score of the cocaine group is 0.42. This outcome indicates that a cocaine CPP was established.

Figure 1 is a summary of results germane to the issue of whether ISR+NTX blocked cocaine's enhancement of a cocaine CPP. The figure shows the means of the cocaine–placebo and cocaine–ISR+NTX groups at baseline and tests 1 and 2. At baseline, and by design, all rats had similar scores. Also, without experiencing cocaine's effects on one side of the alley, scores do not vary across tests (see above, data not presented). So, the best score for comparing cocaine-related scores is either mean baseline of the groups eventually receiving cocaine or mean of all test scores of the groups getting saline during conditioning (mean = 0.31).

The cocaine–placebo group (Fig. 1) showed an enhanced CPP, but the degree of enhancement was not statistically significant: test 1's score = 0.42, test 2's score = 0.51, $t(11) = 1.69$, $p = 0.12$. The Cocaine–ISR+NTX group did not show an enhanced time in the brighter side of the alley, in fact, their

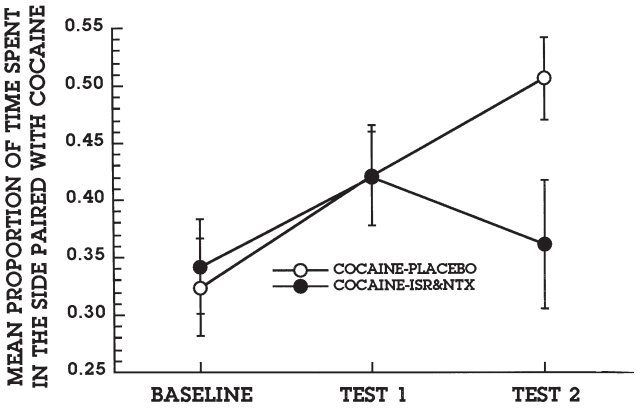

FIG. 1. The two groups, whose scores are depicted here, received the same procedures until test 2. Test 1 was an assessment after pairing cocaine's effects with the brighter side of the alley. Test 2 was similar to test 1 except cocaine was given to both groups. In addition, at test 2, one group received ISR+NTX (closed circles) while the other received the placebo for the combination (open circles). The two groups not receiving cocaine during conditioning (data not presented) had a mean score of 0.31 across all tests. Error bars are standard errors of the means.

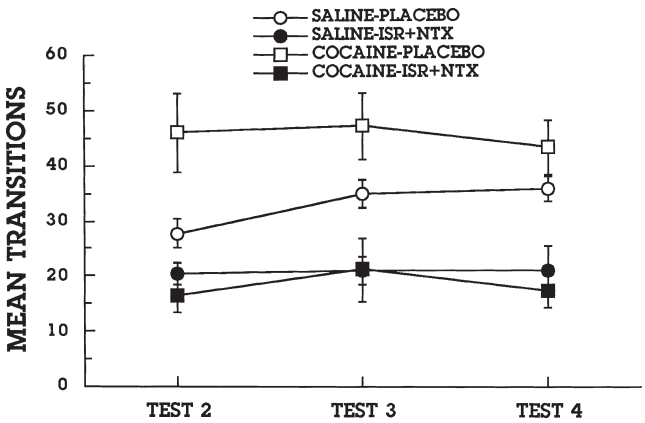

FIG. 2. Mean activity scores, in terms of the number of crosses (transitions) from one side of the alley to the other, for four groups of rats (n = 12). Across tests 2–4, all rats received cocaine just before the test session. Group labels refer to whether the rats received cocaine or saline during conditioning and whether they received ISR+NTX or its placebo across tests 2–4. During baseline and test 1, the mean number of transitions was 25.4 and 26.7, respectively, across all rats. Further, there were no reliable differences between groups (saline vs. cocaine) at baseline or test 1. Error bars are standard errors of the means.

mean score is less than the previous score. A t-test, for dependent measures, of these two groups' test 2 scores yields $t(22) = 2.2$, $p = 0.04$. Another way to assess the effects of ISR+NTX is to compare baseline scores to those of test 2. The mean test 2 scores of the cocaine–placebo group is significantly greater than their mean baseline score, $t(11) = 4.64$, $p = 0.0007$. The same comparison for the cocaine–ISR+NTX group yields $t(11) = 0.27$, $p = 0.79$. In brief, ISR+NTX blocked cocaine's tendency to enhance a cocaine CPP.

Figure 2 presents the data associated with activity for tests 2, 3, and 4. An ANOVA of those data yields, for the factor of ISR+NTX vs. placebo, $F(1, 44) = 30.5$, $p < 0.0001$. That same ANOVA reveals a reliable interaction between history of cocaine dosing and the factor of ISR+NTX vs. placebo, $F(1, 44) = 4.47$, $p = 0.04$. All other factors associated with that ANOVA were not reliable sources of variance (ps > 0.15). Notice that the cocaine–placebo group had the largest activity scores, thereby reflecting sensitization [an ANOVA of the scores of the cocaine–placebo and saline–placebo groups yields a reliable main effect associated with injections of cocaine, $F(1, 22) = 5.41$, $p = 0.03$]. The cocaine–ISR+NTX group did not show heightened activity. Apparently, ISR+NTX blocked all manifestations of cocaine's usual effect of increasing activity.

Separate ANOVAs of the activity data of tests 5 and 6 indicates that the groups' scores were not reliably different from one another. However, the rats, on average, were more active during test 6 compared to baseline, $F(1, 44) = 10.4$, $p = 0.002$, an expected outcome given that all rats received cocaine during some conditioning or testing. In addition, there was a reliable baseline–test 6 by placebo–ISR+NTX interaction. The difference (test 6 minus baseline), in terms of the number of crossings, for subjects receiving the placebo for ISR+NTX is 9.5, whereas the difference for subjects receiving ISR+NTX is 1.4, $F(1, 44) = 5.84$, $p = 0.02$. These data indicate that ISR+NTX muted cocaine's ability to produce conditioned enhancement of activity.

A limitation of this particular experiment is the inability to segregate the effects of blockade of enhanced movement with enhanced positive affect. Because a CPP test usually does not involve giving the drug during the testing for the drug's effects, the test has the advantage of being able to ask questions about affective reactivity unconfounded by motoric effects of the test drug. Here, however, we deliberately confounded enhancement of motor effects with the measure of affect. Regardless of this confound, it seems clear that ISR+NTX produces a fundamental change in the rats' reactivity to cocaine that interacts with a history of experience with cocaine. Also, ISR+NTX has been show to block the establishment of a CPP in another experiment (10).

Experiment 2

Although it is highly unlikely, perhaps ISR+NTX blocks the ability to recall events associated with conditioning. Perhaps, the cocaine-conditioned rats at the critical test 2 of Experiment 1 reacted as saline-conditioned controls, because ISR+NTX blocked recall rather than a critical incentive motivational property of cocaine. This supposition is unlikely, because both calcium channel inhibitors and opioid antagonists have been shown to have no effects on learning and memory or to enhance learning (11,30,33). Nevertheless, to check on the potential for the combination to affect memory, the effects of the dose of ISR+NTX was assessed in a one-trial passive avoidance task.

METHOD

Subjects

The 36 male Sprague–Dawley rats of these procedures were similar to those of the previous procedure. At the start of these procedures, they weighed 337.4 ± 4.76 g (mean ± SEM).

Apparatus

The apparatus was a Plexiglas alley measuring 62 × 28 × 36 cm (L × W × H). One-half of the apparatus was covered with cardboard to make it dark inside that half of the alley.

The opening between the sides of the alley measured 28 by 15 cm (W × H).

Stainless steel rods served as the floor of the apparatus. The grid floor of the dark half of the alley was connected to a scrambled shock source. When shock was administered, it was 1.3 mAmps for no longer than 3 s.

At the start of these procedures, the rats were randomly assigned to be in one of four groups ($n = 9$). The procedures spanned 2 days and involved giving half of the rats ISR+NTX (the same doses as in the previous experiment), and the other half placebos, intraperitoneally, 30 min before each daily session. On the first day, half of the rats received foot shock upon entering the dark half of an apparatus while the others did not.

The amount of time it took for a rat to enter the dark half of the alley on each day of the procedure was tabulated. If, after 180 s a rat failed to enter the dark half of the alley, it was assigned a score of 180 s. The data conform to a $2 \times 2 \times 2$ factorial ANOVA, having repeated measures, with factors associated with (a) ISR+NTX–placebo, (b) shock–no shock, and (c) day 1–day 2.

In addition to these procedures, the latency scores of the groups getting shock and ISR+NTX were again tabulated 3 days after their last injection. If their recall of shock was dependent upon the state produced by ISR+NTX, it would be expected that they would behave as they did at baseline.

RESULTS AND DISCUSSION

The results are presented in Fig 3. The ANOVA of those data reveals reliable main effects associated with shock, $F(1, 32) = 70.0$, $p < 0.0001$, and days, $F(1, 32) = 98.4$, $p < 0.0001$. The ANOVA also revealed a reliable shock by day interaction, $F(1, 32) = 129.5$, $p < 0.0001$. These results were expected, because there is no overlap in distributions of scores between the rats that received shock and those that did not on day 2.

There is no indication in these data that the effects of ISR+NTX differ from those of placebos. No factor of the ANOVA associated with drug effects yielded an F-value indicating a reliable effect, all p-values > 0.29. On day 2, the means of ISR+NTX and placebo groups are equal in the shocked groups and are not statistically significantly different in the no-shock groups, $t(16) = 0.84$, $p = 0.42$.

It should be noted that on day 2 every rat receiving shock on day 1 failed to enter the dark half of the alley and, therefore, received a score of 180 s. It was clear from observing the rats that these rats would not have entered the dark half of the alley even after an extensive period. These rats stayed as far away from the dark half as possible. The rats clearly learned and recalled the events of foot shock regardless of whether they received ISR+NTX or placebos.

The rats of ISR+NTX and foot shock all scored 180 s on their third day of testing. Their recall of events of foot shock did not, evidently, depend on being dosed with ISR+NTX.

There is no basis, in these results, for concluding that ISR+NTX blocked the pain of foot shock, the expression of fear, learning, or memory. Also, the learning transferred from the drugged to the nondrugged state. Because the effects of ISR+NTX did not adversely affect memory, and because there are almost no reasons to suppose they might, it can be concluded that the effects of ISR+NTX in Experiment 1 are not due to the combination blocking memory.

These data lead to the conclusion that ISR+NTX does not have a gross effect on learning and memory. The combination, however, could have subtle effects that this rather insensitive assessment would not index. It may be, for example, that the combination might improve cognitive functioning in some circumstances, and such an improvement would not have been seen with this kind of testing.

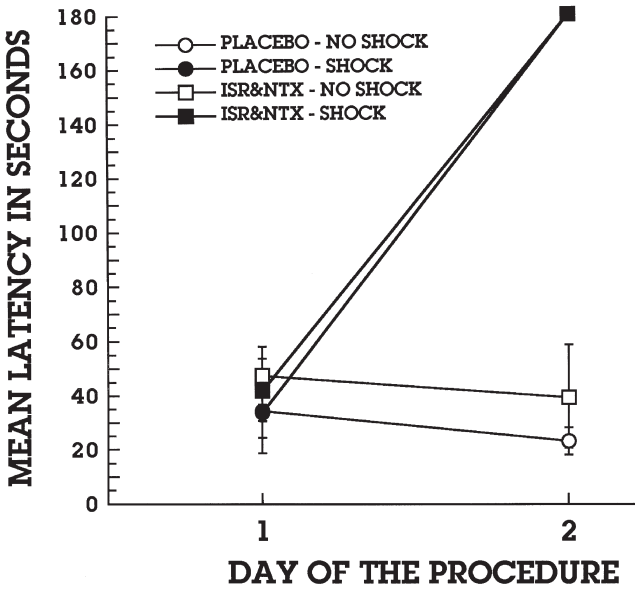

FIG. 3. The mean number of seconds for each of four groups ($n = 9$) of rats to move into a darker side of an alley. On day 1, after entering the darker side, half of the rats were given foot shock and half were not. Before days 1 and 2, half of the rats were given ISR+NTX and the others, placebo. The rats receiving shock clearly learned and recalled the experience of shock, regardless of whether or not they received ISR+NTX. Error bars are standard errors of the means. Note that on day 2, all rats that had received shock had a score of 180 s. Thus, there are no variance estimates associated with the shocked groups on day 2.

GENERAL DISCUSSION

Because there are no pharmacological interventions that have been proven to be successful in treating cocaine use disorders, there is no sure way of knowing directly whether the performance of a putative intervention in any of our animal models is apt to be predictive of success in treating people. All we have to rely on is the apparent reasonableness of our models as derived from modern theories of addiction (7). On those grounds, it seems that a cocaine-induced enhancement of a previously established cocaine CPP would index phenomena germane to cocaine addiction. The results of this experiment, however, indicate that if one wishes to make multiple assessments of a test drug's effectiveness in blocking enhancements that further conditioning needs to be interspersed between tests.

The results provide further support for the conclusion that ISR+NTX will be an effective intervention within a program of treatment for cocaine use disorders. First, ISR+NTX blocked cocaine's ability to enhance a cocaine CPP, and that seems particularly relevant to the drug's ability to prevent relapse into heavy cocaine use. Second, ISR+NTX blocked the expression of cocaine-induced hyperactivity, even among subjects that had previously been sensitized to cocaine's effects. These data combined with the previously collected data (10,24) provide strong support for the conclusion that ISR+NTX fundamentally changes the way cocaine is experienced.

There are a number of limitations to the conclusions that can be drawn from this experiment. The results, for example, are derived from the use of only single doses of cocaine and ISR+NTX. There are, however, other data indicating that a wide variety of doses of ISR combined with doses of NTX are as effective as the doses used here [(24,25); unpublished data] in suppressing cocaine's enhancement of pressing for brain stimulation. Further, this dose of ISR+NTX blocked the enhancement of pressing for brain stimulation usually induced by 20 mg/kg doses of cocaine (unpublished data). So, we can be reasonably sure that the effects are not limited to only these doses.

Although these and other data clearly show that ISR+NTX dramatically modifies the experience usually induced by cocaine, it provides little information about how it might accomplish that change. This dose of ISR+NTX does not, by itself, reduce high levels of pressing for brain stimulation. So, the rats are not debilitated in terms of motor movement. That same result indicates that the rats have the capacity, under ISR+NTX, to experience stimulation-induced affect, thereby, indicating that the system for affect is functional. The doses of ISR and NTX are both small, in terms of behaviorally active doses, and do not either separately or in combination tend to produce signs of malaise or sickness (9,25). In one recently finished experiment, the doses used here were given for over 80 days, and the rats receiving those doses did gain weight regularly and at only slightly reduced rates as those receiving placebos (10). ISR+NTX does not block the ability to learn and recall significant events (Experiment 2). So, maybe ISR+NTX produces it effects in terms other than interfering with the central neural effects germane to cocaine's addictive potential, but it is not obvious how that might be achieved from merely observing the behavior of the rats.

ISR+NTX may prevent the salient effects of stimulants by dampening a positive feedback loop that is normally engaged by events associated with stimulants. There are a number of indications that the endogenous opioid systems are particularly salient to the reinforcing effects of many addictive agents and would be elements in such a positive feedback system. In particular, endogenous opioids seem to be salient to the effects cocaine and similar stimulants (1,2). Recently, we have shown that the selective delta-2 opioid antagonist, naltriben, blocked salient effects of cocaine (22). NTX presumably provides some antagonism at these receptors. NTX has, however, the advantage of already being used by people and advantages in terms of safety and having a long duration of action. Presumably, both naltriben and NTX dampen the secondary effects of a surfeit of dopamine that is associated with cocaine administration.

ISR could dampen the effects of cocaine in a number of ways. ISR might compete with cocaine for the dopamine reuptake site (5). ISR might reduce or slow the release of dopamine. We have recently shown that another agent that inhibits the release of dopamine reduces the reinforcing effect of a stimulant (4). So, the combination may achieve its effects by blocking the elaboration of events usually induced by cocaine.

ISR+NTX also reduce rats' intakes of alcoholic beverage in circumstances that usually sustain large intakes (12). NTX by itself should block the effects of addicting opioids. ISR by itself may be helpful in correcting the hypertension associated with excessive intake of alcohol. ISR may be helpful in correcting the cerebrovascular deficits associated with extensive use of cocaine (15,24,28,31,32). These considerations lead to the conclusion that a combination of ISR and NTX should be an effective medicine for the treatment of polydrug abuse.

ACKNOWLEDGEMENTS

This research was supported by Grant DA 08937 from the National Institute on Drug Abuse. Isradipine was a gift from Novartis and naltrexone from the DuPont-Merck. We appreciate the help of Drs. Engel and Widmer from Novartis and Dr. Rohrback from DuPont-Merck who facilitated these gifts. We thank S. Burgess, C. Cavallaro, L. Gardell, and M. Reid for help in collecting the data of Experiment 2.

REFERENCES

1. Bain, G.; Kornetsky, C.: Naloxone attenuation of the effect of cocaine on rewarding brain stimulation. Life Sci. 40:1119–1125; 1987.
2. Bain, G. T.; Kornetsky, C.: Opioids' modification of central reward processes. In: Reid, L. D., ed. Opioids, bulimia, and alcohol abuse & alcoholism. New York: Springer Verlag; 1990:73–87.
3. Bilsky, E. J.; Montegut, M. J.; Delong, C. L.; Reid, L. D.: Opioidergic modulation of cocaine place preference. Life Sci. 50:85–90; 1992.
4. Bilsky, E. J.; Montegut, M. J.; Nichols, M. L.; Reid, L. D.: CGS 10746B, a novel dopamine release inhibitor, blocks the establishment of cocaine and MDMA conditioned place preference. Pharmacol. Biochem. Behav. (in press).
5. Boja, J. W.; Kopajtic, T. A.: Ion channel inhibitors may function as potential modulators of cocaine binding. Neuropharmacology 32:229–234; 1993.
6. Bozarth, M. A.: Conditioned place preference: A parametric analysis using systemic heroin injections. In: Bozarth, M. A., ed. Methods of assessing the reinforcing properties of abused drugs. New York: Springer Verlag; 1987:241–273.
7. Bozarth, M. A., ed.: Methods of assessing the reinforcing properties of abused drugs. New York: Springer Verlag; 1987.
8. Brogden, R. N.; Sorkin, E. M.: Isradipine: An update of its phamacodynamic and pharmacokinetic properties an therapeutic efficacy in the treatment of mild to moderate hypertension. Drug Eval. 49:618–649; 1985.
9. Calcagnetti, D. J.; Schechter, M. D.: Isradipine produces neither a conditioned place preference nor aversion. Life Sci. 54:81–86; 1994.
10. Cramer, C. M.; Gardell, L. R.; Boedeker, K. L.; Harris, J. R.; Hubbell, C. L.; Reid, L. D.: Isradipine combined with naltrexone persistently reduces the reward-relevant effects of cocaine and alcohol. Pharmacol. Biochem. Behav. (in press).
11. Fulginiti, S.; Cancela, L. M.: Effects of naloxone and amphetamine on acquisition and memory consolidation of active avoidance responses in rats. Psychopharmacology (Berlin) 79:45–48; 1983.
12. Gardell, L. R.; Reid, L. D.; Boedeker, K. L.; Liakos, T. M.; Hubbell, C. L.: Isradipine and isradipine in combination with naltrexone as pharmacotherapy for alcohol dependence. Alcohol. Clin. Exp. Res. 21:1435–1439; 1997.
13. Gerrits, M. A. F. M.; Patkina, N.; Zvartau, E. E.; Van Ree, J. M.: Opioid blockade attenuates acquisition and expression of cocaine-induced place preference conditioning in rats. Psychopharmacology (Berlin) 119:92–98; 1995.
14. Gonzales, P. M.; Boswell, K. J.; Hubbell, C. L.; Reid, L. D.: Isradipine blocks cocaine's ability to facilitate pressing for intracranial stimulation. Pharmacol. Biochem. Behav. 58:1117–1122; 1997.
15. Holman, B. L.; Carvalho, P. A.; Mendelson, J.; Teoh, S. K.; Nardin, R.; Hallgring, E.; Hebben, N.; Johnson, K. A.: Brain perfusion is abnormal in cocaine-dependent polydrug users: A study using Technetium-99m-HMPAO and ASPECT. J. Nucleic Med. 32:1206–1210; 1991.

16. Judson, B. A.; Goldstein, A.: Naltrexone treatment of heroin addiction: One-year follow-up. Drug Alcohol Depend. 13:357–365; 1984.
17. Kosten, T. R.; Kleber, H. D.; Morgan, C.: Role of opioid antagonists in treating intravenous cocaine abuse. Life Sci. 44:887–892; 1989.
18. Kuzmin, A.; Zvartau, E.; Gessa, G. L.; Martellotta, M. C.; Fratta, W.: Calcium antagonists isradipine and nimodipine suppress cocaine and morphine intravenous self-administration in drug-naive mice. Pharmacol. Biochem. Behav. 41:497–500; 1992.
19. Martellotta, M. C.; Kuzmin, A.; Muglia, P.; Gessa, G. L.; Fratta, W.: Effects of the calcium antagonist isradipine on cocaine intravenous self-administration in rats. Psychopharmacology (Berlin) 113:3778–3780; 1994.
20. O'Brien, C. P.; Volpicelli, L. A.; Volpicelli, J. R.: Naltrexone in the treatment of alcoholism: A clinical review. Alcohol 13:35–39; 1996.
21. Pani, L.; Kuzmin, A. V.; Martellotta, M. C.; Gessa, G. L.; Fratta, W.: The calcium antagonist PN 200-110 inhibits the reinforcing properties of cocaine. Brain Res. Bull. 26:445–447; 1991.
22. Reid, L. D.; Hubbell, C. L.; Glick, S. D.; Boswell, K. J.; Chen, A. M.; Moran, C. M.; Cramer, C. M.; Mullen, U. D.; Chambers, M. D.; Gonzales, P. M.; Irizarry, K. L.; Amendola, C. A.: Initial analyses of naltriben, a delta opioid receptor antagonist, as a putative medicine for treating cocaine abuse. Exp. Clin. Psychopharmacol. 4:271–284; 1996.
23. Reid, L. D.; Marglin, S. H.; Mattie, M. E.; Hubbell, C. L.: Measuring morphine's capacity to establish a place preference. Pharmacol. Biochem. Behav. 33:765–775; 1989.
24. Reid, L. D.; Pabello, N. G.; Cramer, C. M.; Hubbell, C. L.: Isradipine in combination with naltrexone as a medicine for treating cocaine abuse. Life Sci. 60:PL119–PL126; 1997.
25. Reid, L. D.; Pabello, N. G.; Gardell, L. R.; Cramer, C. M.; Hubbell, C. L.: Isradipine and naltrexone in combination as a medicine for polydrug abuse. Paper presented at the annual meeting of the International Behavioral Neuroscience Society, San Diego, CA, April 1997.
26. Rossi, N. A.; Reid, L. D.: Affective states associated with morphine injections. Physiol. Psychol. 4:269–274; 1976.
27. Schechter, M. D.; Calcagnetti, D. J.: Trends in place preference conditioning with a cross-indexed bibliography; 1957–91. Neurosci. Biobehav. Rev. 17:21–41; 1993.
28. Spivey, W. H.; Euerle, B.: Neurologic complications of cocaine abuse. Ann. Emerg. Med. 19:1422–1428; 1990.
29. Stapleton, J. M.; Lind, M. D.; Merriman, V. J.; Bozarth, M. A.; Reid, L. D.: Affective consequences and subsequent effects on morphine self-administration of d-ala^2-methionine enkephalin. Physiol. Psychol. 7:146–152; 1979.
30. Tazi, A.; Farh, M.; Hakkou, F.: Behavioral effects of a calcium channel antagonist: Nifedipine. Fundam. Clin. Pharmacol. 5:229–236; 1991.
31. Tumeh, S. S.; Nagel, J. S.; English, R. J.; Moore, M.; Holman, B. L.: Cerebral abnormalities in cocaine abusers: Demonstration by SPECT perfusion brain scintigraphy. Radiology 176:821–824; 1990.
32. Volkow, N. D.; Mullani, N.; Gould, K. L.; Adler, S.; Krajewski, K.: Cerebral blood flow in chronic cocaine users: A study with positron emission tomography. Br. J. Psychiatry 152:641–648; 1988.
33. Wolkowitz, O. M.; Tinklenberg, J. R.; Weingartner, H.: A psychopharmacological perspective of cognitive functions. II. Specific pharmacological agents. Neuropsychobiology 14:133–156; 1985.