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Responding for Rewarding Brain Stimulation: Cocaine and Isradipine Plus Naltrexone

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PABELLO, N. G., C. L. HUBBELL, C. A. CAVALLARO, T. M. BARRINGER, J. J. MENDEZ AND L. D. REID. *Responding for rewarding brain stimulation: Cocaine and isradipine plus naltrexone.* PHARMACOL BIOCHEM BEHAV **61**(2) 181–192, 1998.—Rats, fixed with chronically indwelling electrodes for electrical intracranial stimulation (ICS) of the lateral hypothalamus, were taught to press a bar for ICS. Once pressing rates became stable, during daily 20-min sessions, rats were given cocaine (5 or 20 mg/kg) before the sessions. When given daily, cocaine consistently enhanced rates of pressing. When a combination of small doses of isradipine (e.g., 1 mg/kg) and naltrexone (3 mg/kg) were given before cocaine administration, the combination blocked cocaine's enhancement of pressing for ICS. The combination, however, neither reduced rates of pressing below those observed under placebos (i.e., baseline conditions) nor reduced rates when no cocaine was given. Naltrexone and isradipine (in the dose used in the combination) by themselves did not block cocaine's effects. This profile of effects indicates that a combination of isradipine and naltrexone is apt to be useful in treating cocaine use disorders.

Cocaine Isradipine Naltrexone Fluoxetine Brain stimulation reward Cocaine dependence Cocaine treatment Cocaine abuse Cocaine use disorders

THERE is evidence to support the idea that isradipine (ISR), a calcium channel inhibitor, mutes cocaine's ability to sustain its own use (9,19,31,35,40). Further, there is speculation (48), based on the actions of other calcium channel inhibitors (21,22), that ISR would be beneficial with respect to the focal cerebral vascular deficits accompanying extensive use of cocaine (23,51,54–56). Also, ISR appears to reduce the reinforcing effects of other addictive agents, for example, alcohol and amphetamine (15,43), and, therefore, may be useful in treating polydrug abuse.

Naltrexone (NTX) is a useful pharmacological adjunct to other kinds of treatments for alcohol dependence (36,39,57, 58). NTX, being a selective opioid antagonist, will also block the effects of addicting opioids. NTX also seems to blunt the reinforcing effects of cocaine (5,18,24,27,30).

Recently, we (48) found that a combination of small doses of ISR and NTX (ISR + NTX) reduced cocaine's ability to enhance pressing for intracranial stimulation (ICS). This is a report of further explorations of cocaine and pressing for ICS (Experiment 1) as well as a further explorations of how ISR + NTX (Experiments 3 and 4) might affect that pressing. The procedures of Experiment 2 assess the effects of valproate on cocaine-enhanced pressing for ICS. Also, the effects of NTX by itself and in combination with fluoxetine are described.

EXPERIMENT 1

When rats are fixed with chronically indwelling electrodes for ICS of the medial forebrain bundle (MFB) of the lateral hypothalamus, they can be trained to press a lever for the ICS (37,38). During daily sessions, the rats will press levers for ICS rapidly provided that certain parameters of stimulation are extant (45). When an electrode is properly placed, an ICS, consisting of a series of biphasic pulses continuing for a fraction of a second, will sustain steady pressing. An electrode is "properly placed" when it can be used to activate the MFB and the ICS will sustain pressing without complications such as seizures and apparent ambivalence toward the ICS. A convenient ICS is a train of 60 Hz sine waves of 0.3 s (45).

As intensity of a useful ICS is increased, rate of pressing for ICS is also increased. Further, with electrode tips situated just above or in the MFB, rats work harder for greater intensi-

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ties of ICS up to an intensity producing damage to the tissue at the tip of the electrode (45). Pressing rates are, in general, a function of μcoulombs (μA × seconds) of ICS (26). With a number of sites of ICS, high intensity elicits side effects such as forced motor movements and seizures, which interfere with rapid rates of pressing. This observation, however, should not obscure the general finding that rates of pressing are a function of intensity of ICS.

Drugs that are commonly abused by people, at doses that might be self-administered by rats, lower the intensity of ICS necessary to sustain pressing and increase rates of pressing for ICS. The administration of addictive drugs apparently is the functional equivalent of increasing intensity of ICS; i.e., both addictive drugs and more intense ICS increase functional activity in the MFB system. These relationships are the salient observations for the concepts of modern theories of addiction (6,13,28,29,49,52).

Using rats with chronically indwelling electrodes for ICS of the MFB, we confirm observations, beginning with those of Crow (11), that cocaine increases rates of pressing. Further, in the first procedure, we demonstrate that cocaine's effects, at the doses used subsequently, persist across 11 consecutive daily tests. Results from a second procedure demonstrated that cocaine enhanced responding, without decrement, when given every other day.

METHOD

Subjects

The 9 subjects of the first procedure and the 10 subjects of the second procedure were male Sprague–Dawley rats purchased from Taconic Farms (Germantown, NY) when they weighed about 200 g. When they arrived at the laboratory, they were housed individually in standard hanging cages in a windowless room. The room was maintained at 22 ± 2°C with 12 h of artificial light a day beginning at 0700 h. Food and water were always available in the rats' home cages.

Each rat was fixed with a chronically indwelling bipolar electrode for ICS of the MFB using standard stereotaxic surgical procedures including heavy anesthesia induced by pentobarbital, 50 mg/kg, intraperitoneally given. The electrode was a stainless steel, bipolar electrode, insulated except at the cross sections of the stimulating tips (MS 303/2, Plastics One, Roanoke, VA). The coordinates for the stimulating tips of the electrode were 3.8 mm posterior to bregma, 1.6 mm lateral to the midline, and 8.6 mm ventral to the surface of the skull, with the electrode perpendicular to the horizontal plane between bregma and lambda.

Apparatus

The apparatus was three nearly identical standard Skinner boxes. When a rat depressed a bar, ICS was delivered by way of leads and a slip-ring assembly allowing a rat free movement in its box. ICS was 60 Hz sine waves of 0.3 s train duration of varying intensities, but always less than 40 μA (rms).

Procedure

Five days after recovery from surgery, the subjects were trained to press for ICS. Once a rat was trained to press, intensity of ICS was varied while monitoring rates of pressing to select two intensities of ICS. One intensity, low ICS, was just greater than the minimum necessary to sustain pressing. The other ICS sustained high, but not maximal, rates of pressing (high ICS). Once intensities were selected for a subject, they remained fixed throughout the balance of testing. Across all subjects of this report, the low ICS ranged from 7 to 25 μA (mean = 14.8 μA), while the high ICS ranged from 8 to 30 μA (mean = 18.0 μA). Also, the difference between low and high ICS, across all rats of this report, ranged between 1 and 6 μA.

Once rates of pressing became stable, the rats were allowed to press for ICS for 20 min each day. A daily session involved four consecutive 5-min periods at the high, low, low, and high intensities of ICS (in that order). Each 5-min segment was begun only after a rat self-administered several ICSs at the given intensity. A rat's total presses at each intensity (i.e., number of presses across 10 min) were taken as the data of a day's session.

Subsequent to the establishment of daily testing with the selected intensities of ICS, placebos were administered (injections of the carrier of cocaine). On subsequent days, cocaine was administered. Cocaine HCl (Sigma), in 0.9% physiological saline, was tested at a dose of 5 mg/kg, given 15 min before testing. All injections, in this and subsequent procedures, were given intraperitoneally, 1.0 ml/kg.

The first procedure spanned 16 days. Across days 1–3 and days 15–16, the rats received placebos. Across days 4–14, they received cocaine daily. Thus, there were 16 pairs of scores (number of presses for low and high ICS) for each rat.

A second procedure was very similar to the first one, and assessed the effects of spaced administrations of cocaine on rats' pressing for ICS. Testing spanned 15 days. Across the first and last 3 days, the rats received placebos. Across the middle 9 days, the rats received cocaine, 5 mg/kg, every other day (a total of five doses) and placebo on the intervening days.

RESULTS

Cocaine consistently increased rats' pressing for ICS (Fig. 1). The data of Fig. 1 conform to a 2 × 16 factorial analysis of variance (ANOVA), having repeated measures, with factors associated with intensity of ICS and days of testing, respectively. The ANOVA yields (a) for intensity, $F(1, 8) = 46.1$, $p = 0.0001$, and (b) for days, $F(15, 120) = 10.8$, $p < 0.0000001$. The

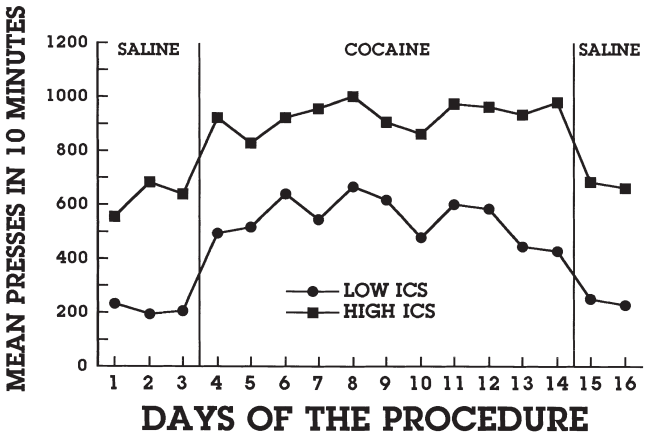

FIG. 1. The effects of cocaine (5 mg/kg) on rats' mean pressing for ICS across 11 consecutive days (days 4–11) are depicted. On days 1–3 and 15 and 16, the rats ($n = 9$) received placebo (saline). Injections were given 15 min before the start of a daily 20-min test session, during which the rats had the opportunity to press for a low and a high ICS for 10 min each. Notice that cocaine persistently facilitated pressing for ICS.

interaction term is not a reliable source of variance, $F(15, 120) = 1.24$, $p = 0.25$.

A 2 × 5 ANOVA of the data associated with the days when placebos were given yields, for Intensity, $F(1, 8) = 104.1$, $p = 0.000007$. Neither the factor of days, $F(4, 32) = 0.50$, $p = 0.73$, nor the interaction, $F(4, 32) = 1.46$, $p = 0.24$, are reliable sources of variance. In brief, rats pressed more for high ICS than low ICS, and pressing was stable across the 5 placebo days, even when measures with cocaine intervened.

When cocaine was given, a similar analysis confirms that rats press more for high ICS, $F(1, 8) = 31.7$, $p = 0.0005$. Under cocaine, daily rates of pressing did not vary markedly, i.e., daily press rates were stable, $F(10, 80) = 1.39$, $p = 0.20$. The values for the interaction are $F(10, 80) = 1.31$, $p = 0.24$.

Because pressing was stable when only placebos were given and when only cocaine was given, the data can be collapsed into a mean across placebo scores and a mean across cocaine scores. When that is done, the results can be characterized as in Fig. 2. Further, because none of the analyses reveal a reliable interaction between intensity of ICS and days of testing, the data can be collapsed into a total score for each condition. Collapsing across intensities, the rats made a mean of 868.1 presses a session under the influence of placebo and 1478.2 presses under cocaine, $t(8) = 7.20$, $p = 0.00009$.

The data of Fig. 3, describing the results of the second procedure, conform to a 2 × 15 ANOVA. The ANOVA yields (a) for intensity, $F(1, 9) = 41.0$, $p = 0.0001$, and (b) for days, $F(14, 126) = 12.0$, $p < 0.0000001$. The value for the interaction term is $F(14, 126) = 0.99$, $p = 0.47$.

A 2 × 10 ANOVA of the data of days on which placebo was given yields, for intensity, $F(1, 9) = 41.3$, $p = 0.0001$. Neither the factor of days, $F(9, 81) = 1.08$, $p = 0.38$, nor the interaction, $F(9, 81) = 1.36$, $p = 0.22$, are reliable sources of variance. In brief, rats pressed more for high than low ICS, and pressing was stable across the 10 placebo days.

A similar analysis of the data of the days when cocaine was given reveals that rats press more for high ICS, $F(1, 9) = 32.8$, $p = 0.0002$ and that, across days of cocaine, rates of pressing were stable, $F(4, 36) = 0.96$, $p = 0.44$. The interaction is not a reliable source of variance, $F(4, 36) = 0.44$, $p = 0.78$. In brief, as expected, rats pressed more for high ICS, and pressing was stable across days when cocaine was given.

Given the outcomes of the analyses, the data can be collapsed into a mean placebo score and a mean cocaine score. On average, the rats made 954.6 presses daily under placebo and 1428.1 presses under cocaine, $t(9) = 6.13$, $p = 0.0002$.

DISCUSSION

Cocaine facilitated rats' pressing for ICS and did so across 11 days (Fig. 1). Also, cocaine always facilitated pressing when given every other day, with no discernible carryover effects (Fig. 3). Notice that the effect of cocaine is analogous to what would happen if the two intensities of the ICS were set higher than usual. In summary, cocaine's facilitation of pressing for ICS is both persistent and consistent, and summarized by the relationship given in Fig. 2.

Given the idea that cocaine's ability to persistently facilitate rats' pressing for ICS is related to cocaines' reward-relevant effects (52), and given that cocaine's abuse-liability is related to its reward-relevant effects (6), it follows that any drug that might block or attenuate cocaine-facilitated pressing for ICS might be useful for treating cocaine abuse.

A drug that blocks cocaine-induced enhanced pressing is one that might be useful for treating cocaine abuse, provided that it did not produce that effect by eliciting toxicity. Thus, a further standard is that the drug should not reduce pressing, when under the influence of cocaine, below rates seen with placebos. Relatedly, a putative pharmacotherapy for cocaine use disorders should not produce marked effects on pressing when no cocaine is given. It is presumed that any drug reducing pressing by itself has considerable potential to produce unpleasant states that are incompatible with using such a drug as a pharmacotherapy for cocaine use disorders.

EXPERIMENT 2

The results of these procedures show that not all drugs having observable behavioral effects block the ability of cocaine to facilitate pressing for ICS. Of course, drugs clearly

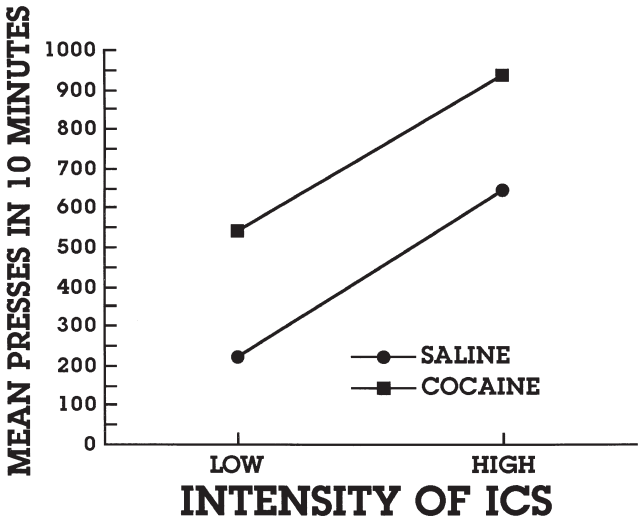

FIG. 2. A summary of the data of Fig. 1 is presented. To obtain these values, all scores reflecting effects of placebo at each intensity were averaged. Also, the mean of all scores reflecting effects of cocaine, at each intensity of ICS, are presented.

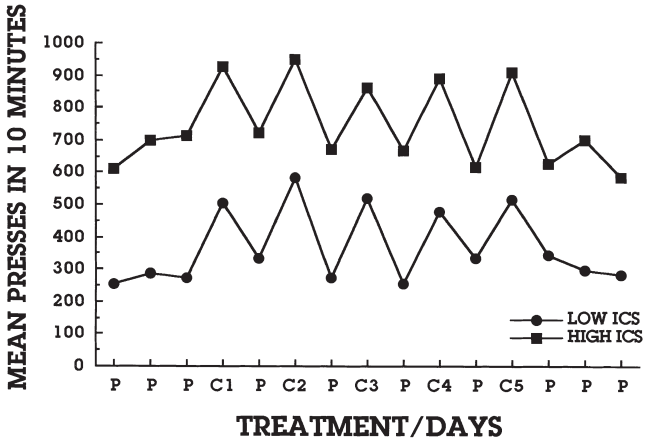

FIG. 3. The effects of 5 mg/kg of cocaine given every other day on five occasions (C1–C5) on rats' mean pressing for ICS. On other days, the rats ($n = 10$) received placebos (P). Notice that pressing for ICS was facilitated, similarly, every time cocaine was given.

having toxic effects will reduce a rat's ability to sustain high rates of pressing characteristic of those seen when cocaine is given. Such toxic effects will probably be manifest in reducing pressing to below baseline levels and be manifest in tests of the drug by itself. An issue, however, remains. Perhaps, the cocaine-induced facilitation in pressing is so fragile that virtually any drug would produce effects seen previously with ISR (19,48).

Because of the similarity between manic episodes of bipolar disorders and the excitation elicited by cocaine, one might conclude that a drug that would reduce mania would be effective in reducing cocaine's enhancing effects on pressing for ICS. Valproate is a drug useful in treating mania (7,8,42). So, it was hypothesized that it would reduce cocaines' effects (depicted in Fig. 1).

In another report, we described the effects of ISR by itself on cocaine-enhanced pressing for ICS (19). Here, we describe the effects of NTX by itself. As mentioned above, there are some indications that NTX might reduce the reinforcing effects of cocaine (5,18,24,27,30). The tests described here using cocaine-enhanced pressing for ICS, however, indicate that NTX by itself may have very limited effects.

As mentioned above, ISR combined with NTX blocks cocaine's reinforcing effects. Perhaps any drug combined with NTX might produce the same effects as combining ISR with NTX. To test that possibility, we conducted tests of fluoxetine combined with NTX.

METHOD

Valproate

The procedures associated with the assessment of valproate are nearly the same as those associated with Fig. 1, except that valproate was given during days when cocaine was given. This dose of valproate is sufficiently large to produce behavioral effects (16). Injections associated with cocaine and valproate were given 15 and 20 min, respectively, before a daily 20-min session. During the daily session, the rats had the opportunity to press for a low and a high ICS for 10 min each.

Three rats were prepared, trained, and were maintained on the daily regimen described in Experiment 1. Testing spanned 24 days. Across days 1–3 and 22–24, the rats received injections of placebo. Across days 4–21, the rats received cocaine daily. In addition to receiving cocaine, the rats also received valproate across the 10-day period spanning days 7–16.

Valproate (valproic acid; 2-propylpentanoic acid sodium salt; Sigma), dissolved in 0.9% saline, was tested in a dose of 200 mg/kg. The dose of cocaine was again 5 mg/kg. Injections associated with valproate and cocaine were given 20 and 15 min before testing, respectively.

Naltrexone

This assessment was similar to the assessment of valproate, except that three doses of NTX HCl (1, 3, and 10 mg/kg) were assessed sequentially. Five rats served as subjects. Each was fixed with an electrode and trained to press for ICS as described previously.

After their pressing was stable, they received two injections daily, one associated with NTX (20 min before the session with ICS), and the other associated with cocaine (5 mg/kg, 15 min before). Initially, the rats received placebos daily (injections of saline, the carrier of both drugs) until pressing was stable for 3 days. Then, they received cocaine daily for the balance of the testing. Once a rat had received cocaine for at least 3 days, each dose of NTX was assessed on a single day. Between tests of a dose of NTX, cocaine was administered for 1–3 days, to assess the potential for carryover effects. Pressing on day (or days) after a dose of NTX were not significantly different from pressing before NTX was given. The doses of NTX were assessed in ascending order across rats.

The following data were common to all rats (for low and high ICS): (a) a 3-day mean placebo score, (b) a 3-day mean cocaine score, and (c) a score associated with each dose of NTX. Those data conform to a 5 × 2 ANOVA, having repeated measures, with factors of treatment (i.e., the placebo, cocaine, and three test scores) and intensity of ICS, respectively.

NTX Combined With Fluoxetine

NTX in combination with fluoxetine HCl (FX) was tested against the ability of cocaine to facilitate rats' pressing for ICS. Eight rats served as subjects. Again, each was fixed with an electrode and trained to press for ICS as described previously.

Two combinations of NTX and fluoxetine were assessed. One (low NTX+FX) involved 5 mg/kg doses of both NTX and FX, and the other (high NTX+FX) involved 10 mg/kg doses of both NTX and FX. The dose of cocaine was, again, 5 mg/kg. The rats received two injections daily, one associated with the combination, and the other associated with cocaine. After 3 days of stable responding under placebos, the rats began getting cocaine. After 3 days of facilitated and stable responding under cocaine, the effects of the combinations were tested on 2 consecutive days. Half the rats received low NTX + FX on the first test day, followed by high NTX+FX on the next. The rest of the rats received the combinations in the opposite order.

Because initial analyses revealed that responding under placebos and under cocaine was stable, mean placebo and cocaine scores were determined. The reduced data conform to a 4 × 2 ANOVA, having repeated measures, with factors of treatment (different drugs) and intensity of ICS, respectively.

RESULTS

The results with valproate are presented in Fig. 4. It is apparent that valproate did not reduce facilitate rats' pressing for ICS. Indeed, the rats made a mean of 1671.3 presses on days when both valproate and cocaine were given, compared to a mean of 1574.6 presses when only cocaine was given.

The results with NTX by itself are summarized in Fig. 5. Clearly, NTX did not block the cocaine's ability to facilitate pressing for ICS, particularly at low ICS. A series of 2 × 2 ANOVAs with factors associated with a specific pair of treatment conditions and intensity of ICS confirm the observation of no marked effects of NTX. Those tests reveal (a) as expected, cocaine facilitated pressing for ICS compared to pressing under placebos, $F(1, 4) = 148.0$, $p = 0.0003$, (b) none of the doses of NTX reliably modified cocaines' effects (all ps > 0.43), and (c) the data associated with each assessment of a dose of NTX were all reliably greater than the data associated with responding under the influence of just placebos (all ps < 0.05).

The results with NTX+FX are presented in Fig. 6. An inspection of the figure indicates that the combination did not reliably reduce pressing. In fact, pressing at low ICS was higher under the influence of cocaine plus the combination than under cocaine plus placebos. Statistical analyses indicate that all values under (a) cocaine plus placebos, (b) cocaine plus low NTX + FX, and (c) cocaine plus high NTX + FX are

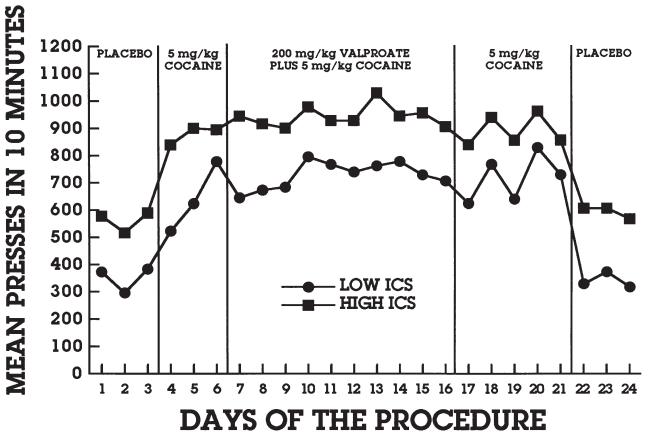

FIG. 4. Depicted are the effects of 200 mg/kg of valproate on the ability of cocaine, 5 mg/kg, to facilitate pressing for ICS among rats (n = 3). Across days 1–3 and 22–24 the rats received injections of saline (placebo). Across days 4–21, the rats received injections of cocaine. Across days 7–16 the rats also received valproate. As expected, cocaine facilitated pressing for ICS. Valproate had no significant effect on cocaine-facilitated pressing. Notice that cocaine persistently enhanced pressing across 18 consecutive days of administration.

greater than their respective values under placebos ($ps < 0.05$). Also, there is no basis for concluding that the corresponding scores of cocaine plus placebo are reliably different from those of cocaine plus the combination of drugs ($ps > 0.23$).

DISCUSSION

Although there were some initial indications from clinical trials that fluoxetine might be helpful in treating cocaine use disorder (3,4,41,59), recent clinical trials do not confirm that initial promise (4,20). These results, and some unpublished data of fluoxetine alone in this kind of test (2), are concordant with human studies showing marginal or no benefit from administering FX. Clearly, not all drugs that are theoretically promising meet standards of either this kind of preclinical screening or those associated with clinical utility.

The results presented in Figs. 4, 5, and 6 represent negative or null effects with respect to valproate, NTX and NTX + FX as pharmacotherapies muting cocaine reinforcement. As such, conclusions that might be drawn are limited as with any data indicating no effect. The small numbers of subjects in each of the tests clearly open the possibility of Type II statistical error. So, the conclusion cannot be safely drawn that valproate, naltrexone, and fluoxetine are inert with respect to cocaine reinforcement. These drugs, however, did not pass the screen.

There is, however, a positive side to these results. The data show that cocaine-induced enhancement of pressing for ICS is not fragile. At the doses used, each of these drugs will reduce rats' intake of alcoholic beverage under circumstances that ordinarily sustain high levels of intake (16,17). So, they do produce measurable effects, but they surely do not readily reduce the enhanced pressing elicited by cocaine. Putative medications do fail to reduce cocaine's reward-relevant effects, even those for which a reasonable rationale can be devised indicating the drug will be useful. These results, therefore, support the idea that a drug that would block cocaine-induced enhancement of pressing for ICS, without reducing pressing below baseline, is apt to be specific to cocaine's effects.

There are a number of tests using rats that might tell us something important about cocaine's ability to sustain its use by people. Procedures involving enhancement of pressing for ICS is one of those tests. Other tests that seem pertinent are those involving cocaine-induced conditioned place preferences and intravenous self-administration of cocaine. Certain assessments of how cocaine is discriminated from cocaine plus a test drug may also be useful. Each of these tests has limitations, and results from each test are helpful in interpreting the outcomes of the others (6).

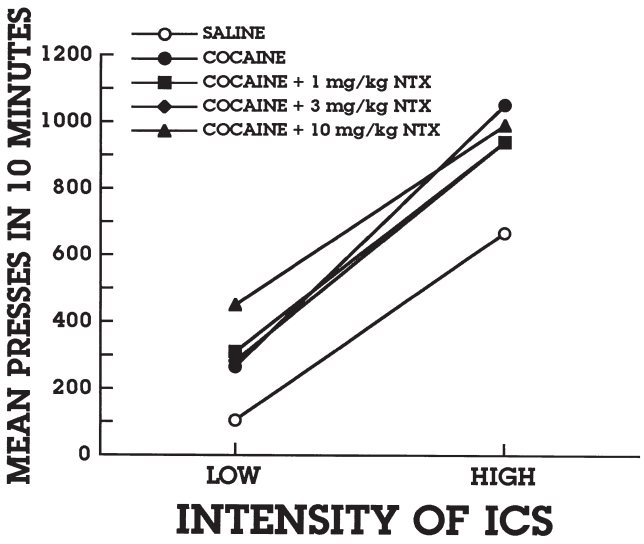

FIG. 5. The effects of three doses of NTX on the ability of 5 mg/kg of cocaine to facilitate pressing for two intensities of ICS among five rats are summarized. As expected, cocaine facilitated pressing. NTX, at the doses tested, did not significantly modify cocaines' effects.

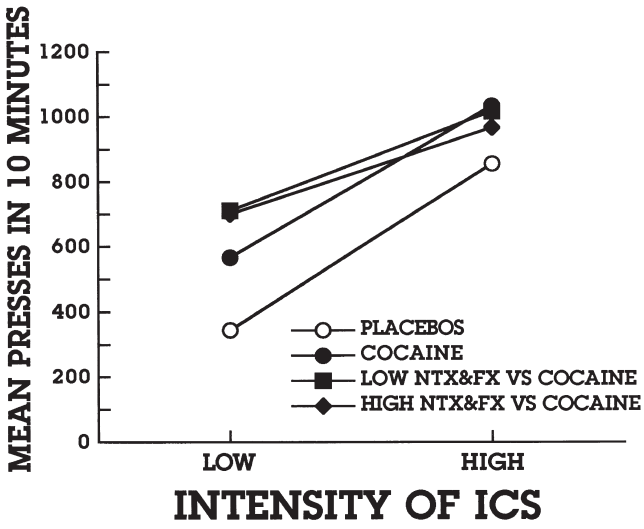

FIG. 6. The effects of combinations of NTX and FX on the ability of 5 mg/kg of cocaine to facilitate pressing for two intensities of ICS among eight rats are summarized. The doses of NTX and FX were 5 mg/kg for low NTX&FX and 10 mg/kg for high NTX&FX. As expected, cocaine facilitated pressing, but neither combination reliably diminished cocaines' effects.

An advantage of using pressing for ICS is that testing also indexes potentially problematic side effects (45). The idea is that a potentially therapeutic drug is one that blocks cocaine's facilitation of pressing, but does not reduce pressing below baseline. A reduction below baseline may index that a test drug is debilitating by way of a variety of mechanisms or that reactivity of the tissue of ICS is reduced to below normal levels. The rat, for example, could be made ill by a test drug. Also, the test drug may interfere with a rat's ability to press by slowing motor movements, producing seizures, hallucinations, or general confusion. Reduced capacity to respond physically or motivationally will surely limit a drug's utility, because problematic features will reduce patients' compliance with the prescription to take the drug. So, the standard that a test drug reduces or blocks cocaine-enhanced facilitation of pressing without reducing pressing below baseline is likely to be a very selective, but predictive, index of utility.

A critic might say that these measures of response rate confound motor, rewarding, and motivational factors. They do, but, as a recent review (53) has noted, it is precisely the integration of these factors that determines the direction and strength of behavior. If the goal is to reduce to nil cocaine's ability to sustain its own use, an agent probably has to interfere with cocaine's multiple effects. Thus, an agent that blocks cocaine's ability to enhance responding for ICS without reducing responding to levels below baseline is also an agent that is apt to interfere with the complex events that sustain cocaine use, but without producing side effects that would interfere with the voluntary taking of the agent. In brief, the goal is to find a drug that will block the ability of cocaine to enhance pressing without reducing the rate of pressing much, if any, below the rate of pressing under placebos.

EXPERIMENT 3

Previously, we (48) gave rats, which were pressing for ICS under the influence of cocaine, the combination of 1 mg/kg of ISR and 3 mg/kg of NTX. We found that the combination blocked cocaine's ability to enhance pressing. These experiments are further tests of this combination of drugs. In one procedure, for example, we extended the dosing for 10 days. The procedures are very similar to those described above involved with the assessment of valproate, except the rats received the combination of 1 mg/kg of ISR and 3 mg/kg of NTX (ISR-1 + NTX-3).

In other procedures, we assessed the combination's effects on the ability of 20 mg/kg of cocaine to facilitate pressing for 5 days. Additionally, the combination by itself was tested on pressing for ICS across 10 days.

ISR, 3 mg/kg, blocked cocaine's ability to facilitate pressing for ICS across 5 days of testing (19). Further, there were indications that a dose of 1 mg/kg of ISR may have blocked cocaine's effects, but there was only a single day of testing. Therefore, we also assessed the effects of 1 mg/kg of ISR on cocaine's facilitation of pressing for ICS across 5 days of testing.

METHOD

The rats of these procedures were fixed with electrodes and trained to press for ICS as described in Experiment 1. ISR-1 + NTX-3 was prepared in a 9.0% Tween 80 (polyoxyethylenesorbitan monooleate), 0.9% NaCl solution. ISR, 1 mg/kg, was also prepared in this vehicle. Cocaine, 5 and 20 mg/kg, was prepared in physiological saline. Injections of drug vehicles served as placebos. Injections of the combination or its vehicle were given 20 min before the daily session. Injections of cocaine or its vehicle were given 15 min before the session. In the assessment of only ISR-1 + NTX-3's effects, the rats only received one injection daily.

In each procedure, the data conform to factorial ANOVAs, having repeated measures, with factors of days, which are associated with drug effects, and Intensity of ICS. In reporting the results of the analyses, we focus on the main effect associated with drug effects. Because, by design, rats press more for high ICS, the factor of intensity of ICS is always a reliable source of variance. Concordantly, we will suspend reporting statistical values for this factor. Similarly, interactions between intensity of ICS and drug effects often do not emerge as reliable factors, i.e., a drug affects rats' behavior similarly across intensities of ICS. Unless an interaction emerges as a reliable source of variance, it is not reported.

ISR-1 + NTX-3 vs. 5 mg/kg Cocaine

Once baseline rates of pressing were stable, six rats began receiving placebos daily. When responding under placebos was stable across, at least, 3 consecutive days, rats began receiving 5 mg/kg cocaine. When responding under cocaine was facilitated and stable across 3 days, the rats began receiving ISR + NTX and cocaine. After 10 days of receiving ISR + NTX and cocaine, there was a 5-day period of just cocaine (and the placebo for ISR + NTX). Finally, there were 4 days with just placebos. Thus, there were 25 days in common for all rats: (a) 3 days of placebo, (b) 3 days of cocaine, (c) 10 days with cocaine and ISR + NTX, (d) 5 additional days of cocaine, and (e) 4 additional days of placebo.

ISR-1 + NTX-3 vs. 20 mg/kg Cocaine

This assessment was similar to the previous one except that testing with the combination spanned 5 days and the dose of cocaine was 20 mg/kg. There were 21 days in common for all five rats: (a) 3 days of placebo, (b) 3 days of cocaine, (c) 10 days with cocaine and ISR + NTX, (d) 6 additional days of cocaine, and (e) 4 additional days of placebo.

ISR-1 + NTX-3

This assessment was similar to the previous two except that here the effects of the combination, by itself, on pressing for ICS were tested across 10 days. There were 16 days in common for all four rats: (a) 3 days of placebo, (b) 10 days with ISR + NTX, and (c) 3 additional days of placebo.

ISR-1 vs. 5 mg/kg Cocaine

This assessment was similar to the previous procedures except that the effects of 1 mg/kg of ISR on the ability of 5 mg/kg of cocaine to facilitate pressing for ICS were assessed. There were 21 days in common for all five rats: (a) 3 days of placebo, (b) 3 days of cocaine, (c) 5 days with cocaine and ISR, (d) 6 additional days of cocaine, and (e) 4 additional days of placebo.

RESULTS

ISR-1 + NTX-3 vs. 5 mg/kg Cocaine

The results are presented in Fig. 7. The ANOVA of those data reveals a reliable main effect of days, $F(24, 120) = 5.18$, $p < 0.0000001$. An analysis associated with the initial and last

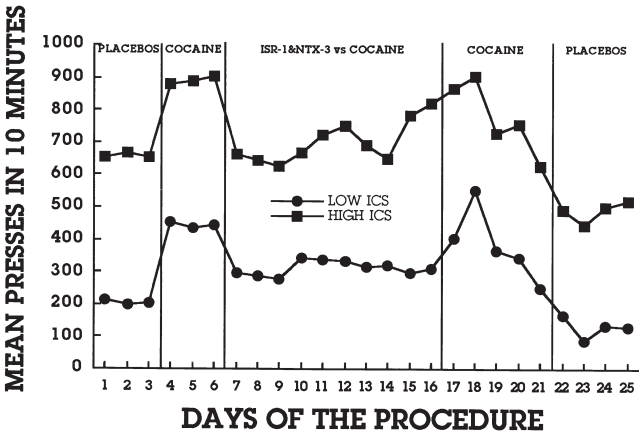

FIG. 7. The effects of the combination of 1 mg/kg of ISR and 3 mg/kg of NTX (ISR-1 + NTX-3) on cocaine (5 mg/kg) facilitated responding for ICS among six rats are depicted. The vertical lines separate the phases of the procedures. As expected, cocaine facilitated pressing for ICS. This effect was blocked by ISR+NTX. Further, the effect of ISR+NTX was sustained across 10 days.

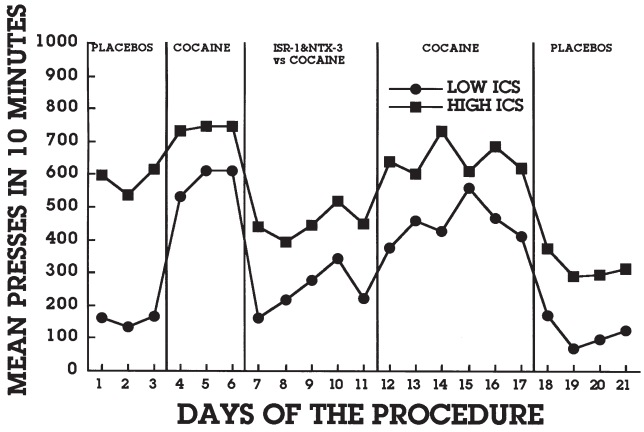

FIG. 8. The results of assessing the effects of the combination of 1 mg/kg of ISR and 3 mg/kg of NTX (ISR-1 + NTX-3) on the ability of 20 mg/kg of cocaine to facilitate pressing for ICS among five rats are depicted. Notice that this dose of cocaine facilitated pressing and that ISR+NTX blocked that effect.

days of placebos (days 1–3 and 22–25) revealed that responding during those periods was similar, $F(1, 5) = 2.55$, $p = 0.17$. A similar analysis revealed that responding during the last cocaine days (days 17–21) was similar to that during the initial days with cocaine (days 4–6), $F(1, 5) = 2.41$, $p = 0.18$. The data of the days following the 10-day period of testing with ISR+NTX are not considered further here.

A series of ANOVAs, with factors of days and intensity of ICS, revealed that responding was stable across the initial 3 placebo days, $F(2, 10) = 0.06$, $p = 0.94$, the initial 3 cocaine days, $F(2, 10) = 0.09$, $p = 0.91$, and the 10 test days with ISR + NTX and cocaine, $F(9, 45) = 0.80$, $p = 0.62$. There was some slight deterioration of pressing during the last administrations of cocaine that carried over to the final days with placebos, but as noted above, these effects were not large.

A 2 × 2 ANOVA with factors of treatments and intensity of ICS of the 3-day mean placebo and cocaine scores confirms that cocaine facilitates responding for ICS, $F(1, 5) = 116.8$, $p = 0.0001$. Similar analyses reveal that the mean 10-day test scores are reliably less than the mean cocaine scores, $F(1, 5) = 7.81$, $p = 0.04$, and not reliably different than the mean placebo scores, $F(1, 5) = 2.05$, $p = 0.21$.

ISR-1 + NTX-3 vs. 20 mg/kg Cocaine

Figure 8 presents the results associated with 20 mg/kg of cocaine. The ANOVA of those data reveals a reliable main effect of days, $F(20, 80) = 12.1$, $p < 0.0000001$. Pressing was stable across initial days with placebos (days 1–3), across initial days cocaine (days 4–6), and across the 5-day period of testing with ISR + NTX. Thus, we reduced the data into mean placebo, cocaine, and test scores.

The reduced data conform to a 3 × 2 ANOVA with factors of treatments and intensity of ICS, respectively. That ANOVA reveals reliable sources of variance associated with each of the main effects and the interaction (all ps < 0.003). Tests for simple main effects revealed that (a) 20 mg/kg of cocaine facilitated pressing, $F(1, 4) = 84.5$, $p = 0.0008$, (b) ISR + NTX blocked cocaine's effect on pressing, $F(1, 4) = 15.3$, $p = 0.01$, such that, (c) rats' mean rate of pressing during testing with ISR + NTX was not different than during only placebos, $F(1, 4) = 0.11$, $p = 0.76$. Once again, we saw some slight deterioration of pressing toward the end of dosing with cocaine that carried over to the final days with placebos, particularly at high ICS (see Table 1).

ISR-1 + NTX-3

Figure 9 presents the results associated with the effects of ISR + NTX on pressing for ICS. The ANOVA of those data reveals a reliable interaction term, $F(15, 45) = 1.93$, $p = 0.05$. The factor of days of testing is not a reliable source of variance, $F(15, 45) = 1.22$, $p = 0.29$.

Subsequent analyses revealed that pressing was stable across days with placebos (days 1–3 and 14–16), and across the 10-day period of testing with ISR + NTX. Thus, we re-

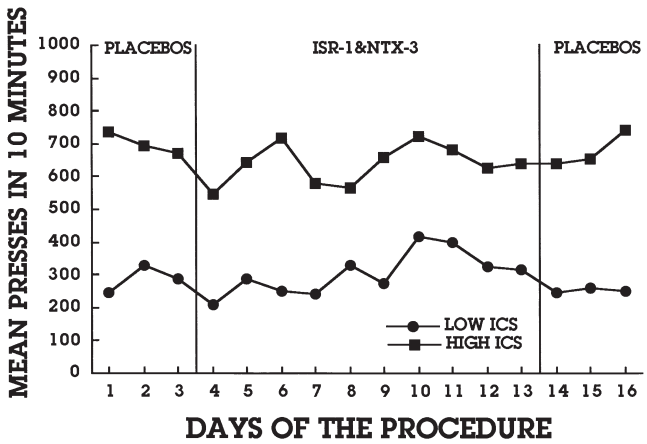

FIG. 9. The effects of the combination of 1 mg/kg of ISR and 3 mg/kg of NTX (ISR-1+NTX-3) on pressing for ICS among four rats are depicted. In brief, ISR+NTX had no discernible effect on pressing.

duced the data into mean placebo and test scores. The reduced data conform to a 2 × 2 ANOVA with factors of treatment and intensity of ICS, respectively. The factor of treatment and the interaction term were not reliable sources of variance ($ps > 0.18$).

The analysis of the data of the 10-day period of ISR + NTX yielded a reliable interaction term, $F(9, 27) = 2.31$, $p = 0.04$, suggesting that the source of the reliable interaction term revealed by the overall ANOVA was during this 10-day period. Subsequent analyses did not discern the source of the reliable interaction. For example, within each intensity of ICS, Students' *t*-tests, for dependent measures, comparing the scores of the first test day with each of the subsequent test days failed to reveal any reliable differences. It is concluded that this interaction can be ignored because, although it meets standards of statistical significance, it does not appear to be meaningful when looking at the rats' day-to-day behavior, as depicted in Fig. 9.

ISR-1 vs. 5 mg/kg Cocaine

Figure 10 presents the results associated with the effects of 1 mg/kg of ISR on the ability of 5 mg/kg of cocaine to facilitate pressing for ICS. The ANOVA of those data reveals a reliable main effect of days, $F(20, 80) = 2.29$, $p = 0.005$. Although an inspection of Fig. 10 indicates that ISR may have affected pressing more at high ICS than low ICS, the interaction term is not a reliable source of variance, $F(20, 80) = 1.50$, $p = 0.11$.

Subsequent analyses revealed that pressing was stable across initial days with placebos (days 1–3), across initial days cocaine (days 4–6), and across the 5-day period of testing with ISR + NTX (all $ps > 0.08$). Thus, we reduced the data into mean placebo, cocaine, and test scores.

As expected, cocaine facilitated pressing, $F(1, 4) = 68.5$, $p = 0.001$. Pressing under ISR, on average, was not reliably different to that under cocaine, $F(1, 4) = 2.68$, $p = 0.18$, or placebo, $F(1, 4) = 0.13$, $p = 0.73$. In brief, pressing under ISR was intermediate to that under placebo and cocaine.

Once again there was a reduction in pressing following multiple days of cocaine, but the differences between initial (days 4–6) and last (days 12–17) cocaine scores are not statistically significant (a test for simple main effects yields $p > 0.13$).

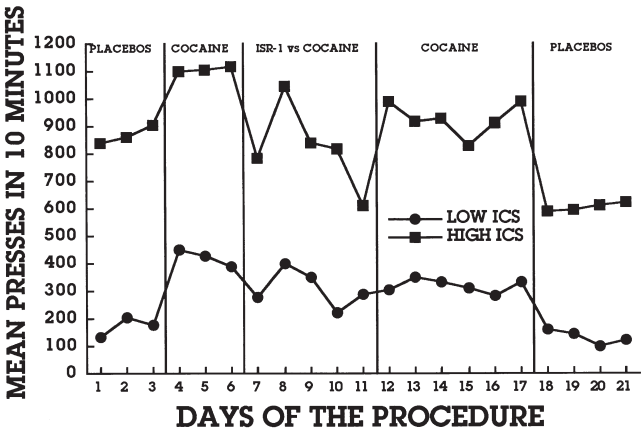

FIG. 10. The results of assessing the effects of 1 mg/kg of ISR (ISR-1) on the ability of 5 mg/kg of cocaine to facilitate pressing for ICS among five rats are depicted.

EXPERIMENT 4

In Experiment 3, ISR-1 + NTX-3 blocked the ability of 5 and 20 mg/kg of cocaine to facilitate pressing for ICS. Those results replicate and extend our previous research (48). However, the data are limited by the fact that only one "dose level" of the combination has been assessed extensively. In this experiment, the effects combining 3 mg/kg of ISR with 3 mg/kg of NTX (ISR-3 + NTX-3) were assessed (a) on the ability of 5 mg/kg of cocaine to facilitate pressing for ICS daily, and (b) by itself on daily pressing for ICS. In general, these procedures are similar to those of the previous experiments.

METHOD

The five rats of the procedure assaying ISR-3 + NTX-3 on cocaine's effects were fixed with electrodes and trained to press for ICS, as described in Experiment 1. Procedures involving daily injections were similar to those of Experiment 3. Once rats' baseline rates of pressing at both intensities of ICS were stable, they began receiving daily injections. There were 17 days in common for all rats (a) 3 days of placebo, (b) 3 days of cocaine (5 mg/kg), (c) 5 days with cocaine and ISR-3 + NTX-3, (d) 3 additional days of cocaine, and (e) 3 additional days of placebo.

The four rats of the procedure assessing ISR-3 + NTX-3 were treated as those of the other experiments. There were 11 days of testing (a) 3 days of placebo, (b) 5 days with ISR-3 + NTX-3, and (c) 3 additional days of placebo.

RESULTS

ISR-3 + NTX-3 vs. 5 mg/kg Cocaine

The results are presented in Fig. 11. The ANOVA of those data reveals a reliable main effects of days, $F(16, 64) = 5.05$, $p = 0.00001$. An analysis of the data associated with the initial days of placebos (days 1–3) with that of the last days of placebos (days 15–17) revealed that responding during those periods was similar, $F(1, 4) = 0.15$, $p = 0.72$. A similar analysis

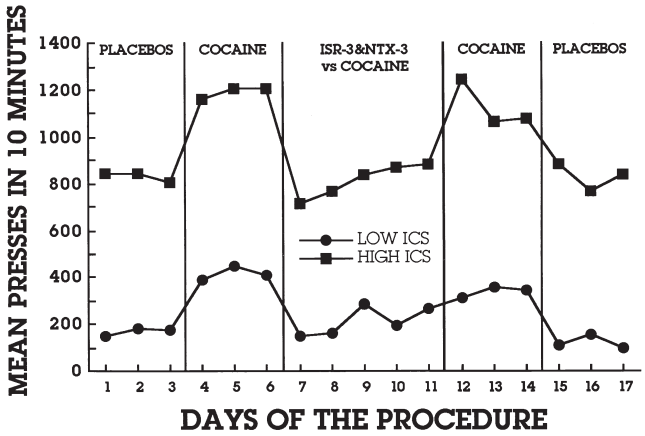

FIG. 11. The effects of the combination of 3 mg/kg of ISR and 3 mg/kg of NTX (ISR-3+NTX-3) on cocaine (5 mg/kg) facilitated responding for ICS among five rats are depicted. The vertical lines separate the phases of the procedures. As expected, cocaine facilitated pressing for ICS. This effect was blocked by ISR+NTX. Further, the effect of ISR+NTX was sustained across 5 days.

revealed that responding during the last days with cocaine (days 12–14) was similar to that during the initial days with cocaine (days 4–6), $F(1, 4) = 3.60$, $p = 0.13$. Thus, the data associated with the days following the 5-day period of testing with ISR + NTX are not considered further here.

A series of ANOVAs, with factors of days and intensity of ICS, revealed that responding was stable across the (a) placebo days, $F(2, 8) = 0.38$, $p = 0.69$, (b) cocaine days, $F(2, 8) = 3.39$, $p = 0.09$, and (c) test days with ISR + NTX and cocaine, $F(4, 16) = 1.27$, $p = 0.32$.

A 2 × 2 ANOVA with factors of treatment and intensity of ICS of the 3-day mean placebo and cocaine scores confirms that cocaine facilitates responding for ICS, $F(1, 4) = 163.9$, $p = 0.0002$. Similar analyses reveal that the mean 5-day test scores (cocaine plus ISR-3 + NTX-3) are reliably less than the mean cocaine scores, $F(1, 4) = 13.1$, $p = 0.02$, and not reliably different than the mean placebo scores, $F(1, 4) = 0.02$, $p = 0.89$.

ISR-3 + NTX-3

Figure 12 presents the results associated with the effects of ISR + NTX on pressing for ICS. The ANOVA of those data reveals a reliable main effect of days, $F(10, 30) = 2.70$, $p = 0.02$. Pressing was stable across days with placebos (days 1–3 and 9–11), and across the 5 days with ISR + NTX (all ps > 0.06). Thus, we reduced the data into mean placebo and test scores.

The reduced data conform to a 2 × 2 ANOVA with factors of treatment and intensity of ICS, respectively. The factor of treatment and the interaction term were not reliable sources of variance (ps > 0.15).

As mentioned, the overall ANOVA revealed a reliable source of variance associated with days of the procedure. Subsequent analyses support what is apparent from inspection of Fig. 12. Specifically, on the first test day, pressing for high ICS was reliably reduced compared to mean pressing for high ICS under placebo, $t(3) = 4.20$, $p = 0.02$. No other test scores were reliably different from the respective mean placebo scores.

DISCUSSION

Because of the logical limitations, the conclusion cannot be drawn that combinations of ISR and NTX have no effect on pressing for ICS. Further, there are indications that ISR, at doses used in these experiments, does produce a small reduction in pressing on the first day of its administration. The reductions that are seen with ISR and ISR + NTX, however, seem to be transitory and, at best, small.

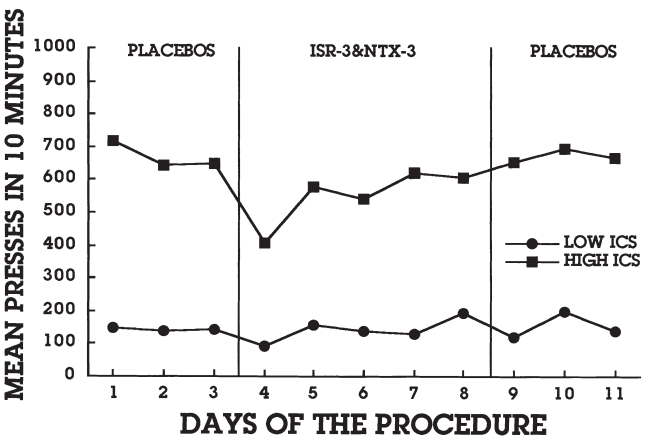

FIG. 12. The effects of the combination of 3 mg/kg of ISR and 3 mg/kg of NTX (ISR-3+NTX-3) on pressing for ICS among four rats are depicted. In brief, ISR+NTX had very little effect on pressing for ICS.

Although the data are limited, it does appear that there is a considerable range of doses of ISR + NTX that will block a range of doses of cocaine [(48); these experiments; and unpublished data]. Further, there appears to be a range of doses of ISR + NTX that produce limited, or no significant, effects on pressing for ICS when no cocaine is given. Given that there is a broad range of potentially effective doses, it is likely that doses can be selected to be used with people.

GENERAL DISCUSSION

The initial administrations of cocaine may appear to produce more stable responding than subsequent administrations of cocaine (Figs. 4, 7, 8, 10, and 11). This may, however, be an artifact of the procedure. The initial days under cocaine are somewhat selected. The practice of requiring 3 days of stable responding under cocaine before assessing a test drug is a good experimental procedure, allowing the use of fewer subjects, but it does mask some variability associated with cocaine's initial effects. Once ISR or ISR + NTX were given, however, every score became part of the data for analyses. The same kind of procedural effect may mask some variability in the initial placebo scores, because once again further testing is begun only after apparent stability.

The results of Experiment 1 confirm that cocaine increases pressing for ICS. Cocaine increases pressing at nearly all intensities except the very highest. At higher, but nonlesioning intensities, ICS-induced events can be evoked that interfere with high rates of pressing such as seizures, forced motor movements, or excessive autonomic activity (45). The result is that intensity by rate functions often appear to be inverted U-shaped curves. There are also complications associated with measuring the enhancing effects of cocaine and with measuring cocaine's effects on the usually unspecified factors that decrease rates of pressing when moving from a high intensity to a very high intensity. To avoid these complications, we almost always choose intensities producing considerably less than maximal pressing.

If intensities are chosen that are between those just more than threshold for sustaining some pressing but less than maximal responding, there appears to be no advantage to using more than a single intensity in initial screening tests. With intensities such as those used here, there is seldom a reliable interaction between intensity and another variable [(25); these experiments].

Screening procedures should allow the rapid assessment of potential drugs. Using the procedure of every other day with cocaine (Fig. 3) and a single intensity of ICS sets the conditions for assessing a drug rapidly. If a tested dose is given across a few days while cocaine is administered every other day, then the doses' effects on pressing with and without cocaine are assessed. Both sets of data (the drug's effects on cocaine-enhanced pressing and pressing by itself) are acquired more rapidly than the same kind of data were acquired in Experiments 2, 3, and 4.

With some procedures, it appears that daily dosing with cocaine leads to a reduction in reactivity to ICS. That reduction probably reflects some reduced functionality of the MFB system. Presumably, a manifestation of reduced functioning of the MFB system would be (a) a reduction in cocaine's abil-

ity to induce positive affect, and (b) in the noncocaine condition, a propensity toward depression and an amotivational syndrome. For example, there are reports (32–34) indicating that self-administration of large doses of cocaine leads to less responsiveness to ICS.

With respect to these smaller doses of cocaine given daily, a question is whether, on average, postcocaine-placebo scores are less than precocaine-placebos scores and whether any differences that are seen might be due to chance. Table 1 is a tabulation of the results of the various procedures reported here. The means were derived by averaging across all precocaine-placebos scores (across days and intensities of ICS) and across all postcocaine-placebo scores of Figs. 1, 4, 7, 8, 10, and 11. The mean of all preplacebos scores is 445 presses in 10 min, while the mean for postplacebos scores is 384. Given that the mean of some postcocaine-placebo scores are greater than their respective precocaine-placebo scores, the decrease will not meet standards of statistical significance. Nevertheless, notice, from Table 1, that the experiment involving 20 mg/kg dose of cocaine (Fig. 8) produced the largest reduction in pressing and the relevant difference nearly meets criterion for statistical significance. Further testing might reveal that daily dosing with rather small doses of cocaine can eventually lead to a reduction in reactivity of the MFB system.

ISR, 1 mg/kg, produced only slight or no reduction in cocaine-enhanced pressing [(19) and Experiment 3]. There are indications that opioid antagonists can mute some stimulants' effects (1,5,18,25,30,46,47). Nevertheless, at the doses used in these procedures, NTX by itself did not produce reliable reductions in cocaine-enhanced pressing (Experiment 2). The conclusion is that neither ISR nor NTX, at doses ISR-1 + NTX-3, are effective by themselves.

These data confirm and extend the initial indications (48) that combinations of ISR and NTX block cocaine's effects. The initial results are reliable, i.e., they can be replicated again and again. The results reported here indicate that the effects of the combination in blocking cocaine's effects do not wane with repeated administrations, and that a larger dose of ISR may be used in the combination and still meet standards in as much as its negative effect may wane after a few doses. Also, the combination is effective when large doses of cocaine are administered. Further, the data indicate that other putative drugs for treating cocaine use disorders do not produce similar effects.

TABLE 1
EFFECTS POST COCAINE

Figure	N	Pre	Post	t	p
1	9	420	455	−0.68	0.52
4	3	456	466	−0.15	0.89
7	6	432	309	1.60	0.17
8	5	370	218	2.68	0.06
10	5	521	368	2.39	0.08
11	5	499	475	0.38	0.72

Pre and post refer to the mean number of presses made under the influence of placebos (across days and intensities of ICS) at the beginning and end of the procedures depicted in Figs. 1, 4, 7, 8, 10, and 11. In each procedure, there was a 5- or 10-day period during which rats received injections of cocaine (5 or 20 mg/kg) between the pre- and post-placebo days. The values are from dependent *t*-tests.

These data indicate that if cocaine is taken while a patient is under the influence of ISR + NTX, cocaine will not achieve its usual reinforcing effects. Consequently, ISR + NTX is apt to emerge as a medicine useful in treating cocaine use disorders.

As part of a comprehensive treatment program for alcohol use disorders, NTX has the effect of preventing relapse back into excessive drinking of alcoholic beverages (39,57,58). Consequently, NTX is apt to control the excessive drinking of the typical patient presenting with cocaine use disorders. This, in turn, is apt to control certain kinds of impulsive behavior that seem to emerge with alcohol intoxication, including relapse to cocaine use. Further, ISR by itself may be helpful in treating alcohol use disorders (12,14,50). The combination was effective in reducing propensity to take alcoholic beverages among rats (10,15) using the same procedures that indicate that NTX is effective (44). Presumably, reduced instances of alcohol use would also reduce instances of cocaine use.

There are indications that cocaine produces cerebral vascular deficits (23,54–56). ISR is apt to be therapeutic with respect to these vascular difficulties (48). Further, ISR will be helpful with respect to the hypertension that accompanies alcohol use disorders. NTX will block the positive reinforcing effects of sampling addicting opioids. So, ISR + NTX, in addition to blocking cocaines' reinforcing effects, has a favorable side effect profile.

There is a preference for using only one drug as a medicine for a particular problem. This preference is based on the idea that when two drugs are used there are, potentially, problematic side effects of each drug plus those that emerge from their interaction, or, stated differently, just too many potential problems. It may be, for example, that large doses of ISR can achieve much the same result as the combination of small doses of ISR and NTX (15). Larger doses of ISR than those used here, however, do lead to hypotension, which may be a limiting side effect (10,15).

There is a problem with the prescription to take any drug for a prolonged period of time, and that problem is particularly salient with drugs designed to stem the use of addictive drugs. The problem involves issues associated with daily compliance with the prescription. To achieve a greater chance of compliance, the usually small, but nevertheless problematic side effects that accompany using drugs need to be reduced to a bare minimum. Instances of side effects and more severe side effects usually emerge with larger doses of a drug. So, the idea is to use the minimally effective dose of a drug. Unfortunately, it is usually unknown what is the minimally effective dose for a given individual. So, the usual dose is one that tends to surely be large enough to achieve the desired effect, but also one that may elicit side effects.

Because of a reduced potential for side effects, ISR + NTX may have an advantage. Even though, generally, more side effects emerge with a combination of drugs, there is the possibility that using small doses of two drugs will produce fewer side effects than using larger doses of one drug. Larger doses of ISR, for example, produce signs of hypotension [rats drink more supposedly due to apparent hypovolemia due to low blood pressure (15)]. Combining a low dose of ISR with NTX is not only effective, but reduces the side effect manifest as increased drinking associated with an effective but larger dose of ISR. So, even though two drugs are used, the induced side effects can be smaller than when only one is given.

The issues associated with doses are particularly relevant when thinking about the doses that might be used with people. Both ISR and NTX will probably be taken orally by patients. Further, if ISR is taken twice daily in doses that are

usually given to treat hypertension and NTX is taken once daily in doses that are used to treat alcohol dependence, the expectation is that, after some days, there will be some levels of drugs in the plasma throughout the day. This condition of constantly circulating drug is different than the condition of these tests, even though drugs were given daily. The conclusions derived from these data provide the rationale for further testing with people, including pharmacokinetic analyses.

In summary, these data confirm that small doses of ISR combined with small doses of NTX reduce cocaine's ability to enhance pressing for ICS (48). A drug reducing cocaine's ability to enhance pressing for ICS without reducing pressing to below baseline rates will, it is believed, reduce cocaine's ability to sustain its own use without producing depression or a general malaise. These findings also indicate that ISR + NTX's effects will persist when given day after day, even though these tests extended for only 10 days [other tests (10) extended for more than 60 days]. These conclusions are concordant with conclusions derived from recently collected data indicating that ISR + NTX will block cocaine's ability to establish a conditioned place preference (10). These data compliment data indicating that ISR + NTX is apt to be useful in treating alcohol use disorders. When given to people, these drugs, individually, are known to be safe when given day after day. Collectively these findings, with the possibilities for a favorable side effect profile, indicate that ISR + NTX would be an effective medicine for polydrug abuse in which cocaine is the focus of problematic drug use.

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