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Isradipine Blocks Cocaine's Ability to Facilitate Pressing for Intracranial Stimulation

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GONZALES, P. M., K. J. BOSWELL, C. L. HUBBELL AND L. D. REID. *Isradipine blocks cocaine's ability to facilitate pressing for intracranial stimulation*. PHARMACOL BIOCHEM BEHAV **58**(4) 1117–1122, 1997.—Using rats pressing for rewarding electrical intracranial stimulation of the medial forebrain bundle, it was found that a single administration of isradipine blocked the rate-enhancing effects of cocaine (5.0 mg/kg) at doses of 3.0 and 10.0 mg/kg. Also, when isradipine (3.0 mg/kg) was administered alone (without cocaine) for 5 consecutive days, pressing for intracranial stimulation was not reduced relative to placebo levels. In another experiment, isradipine (3.0 mg/kg) persistently blocked the rate-enhancing effects of cocaine (5.0 mg/kg) across 5 consecutive days. These results support the continued investigation of isradipine as a useful adjunct to other treatments for cocaine addiction. © 1997 Elsevier Science Inc.

Cocaine Reward Intracranial stimulation Isradipine

RECENT evidence suggests that calcium channel blockers (CCBs) decrease the reinforcing properties of addictive agents (3–5,10,11,13,15–17). Isradipine (ISR), a representative of the 1,4-dihydropyridine class of CCBs, for example, inhibits the apparent rewarding properties of cocaine (COC) in place preference conditioning (13) and self-administration tests among rodents (10,11). It has also been reported that nifedipine, another member of the dihydropyridine class of CCBs, attenuates cocaine's subjective effects among people (12). On the other hand, diltiazem and verapamil, representatives of the benzothiazepine and phenylalkylamine classes of CCBs, respectively, were not effective in reducing COC self-administration among squirrel monkeys (19). In the same study, nimodipine, a CCB of the same class as ISR, also did not reduce COC self-administration. Further study of ISR seems warranted.

A reliable index of COC's reinforcing effects is its ability to facilitate rates of pressing for electrical, intracranial stimulation (ICS) of the medial forebrain bundle (9,14). It has been shown that almost all addictive agents commonly abused by people, including COC, enhance responsiveness for rewarding ICS in rats. It follows that any agent that might block COC's ability to enhance responding for ICS might also block COC's positively reinforcing features. To further investigate the possibility that ISR can attenuate the positive affective properties of COC, the experiments reported here assessed ISR's ability to suppress COC's enhancement of pressing for ICS.

GENERAL METHOD

Subjects

The subjects of all procedures were male, Sprague–Dawley rats weighing 200–225 g when purchased from Taconic Farms (Germantown, NY). Upon arrival at the laboratory, they were housed, individually, in standard, stainless steel, hanging cages in a windowless colony room maintained at 22 ± 2°C with 12 h a day of incandescent lighting beginning at 0700 h. The subjects had free access to food and water at all times in their home cages.

Surgery

Each rat was fixed with a chronically indwelling bipolar, stainless steel electrode (MS 303/2, Plastics One, Roanoke, VA) for stimulation of the medial forebrain bundle at the level of the lateral hypothalamus using standard stereotaxic procedures, including deep anesthesia (induced by 50 mg/kg pentobarbital sodium, given intraperitoneally). The electrode

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wires were insulated except at the cross sections of the tips. The stereotaxic coordinates for the electrode tips 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 shaft perpendicular to the horizontal plane between bregma and lambda. Subjects were allowed at least 5 days to recover from surgery.

Apparatus

Three nearly identical standard operant chambers were used. The leads from the ICS-generator connected to the rat by way of a slip-ring assembly, thereby allowing a rat to move freely in the chamber. A press of the lever resulted in an ICS of 60 Hz sine waves of 0.3 s of varying intensities, but always less than 50 μA (rms). If a rat pressed during an ICS, that press was recorded, but no additional ICS was delivered.

Drugs and Injections

COC HCl (Sigma) was tested in a dose of 5.0 mg/kg. COC was dissolved in physiological (0.9%) saline. Injections of saline served as placebos. COC and placebo were administered intraperitoneally, in a volume of 1.0 ml/kg, 15 min before testing.

ISR [Sandoz; in 9% Tween 80 (polyoxyethylene sorbitan mono-oleate)] was tested in doses of 1.0, 3.0, and 10.0 mg/kg. ISR and its placebo (vehicle for ISR) were administered subcutaneously in volumes of 1.0 ml/kg, 20 min before testing.

Procedure

After recovering from surgery, rats were trained to press a lever to receive ICS. Only subjects that readily learned to press were retained for further study. Once a rat had learned to press, the intensity of ICS was varied, while monitoring rates of pressing, to select two intensities. One intensity (low ICS) was just greater than the minimum necessary to sustain pressing. An intensity greater than low ICS sustained higher, but not maximal, rates of pressing (high ICS).

Once intensities were selected for a subject, they remained fixed throughout subsequent testing. Once rates of pressing became stable at the selected intensities, a rat was tested daily, for about 20 min. A daily test was 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.

EXPERIMENT 1

In this experiment, the effects of ISR, 1.0, 3.0, and 10.0 mg/kg, on COC's facilitation of pressing for ICS were assessed. Given the results of Kuzmin et al. (10), Martellota et al. (11), and Pani et al. (13), it is hypothesized that ISR at the higher doses would reduce COC's ability to facilitate pressing for ICS. If that is, indeed, the outcome of testing, such a finding would provide additional support for the idea ISR blocks COC's reward-relevant effects.

METHOD

Upon recovery from surgery, the 6 rats of this procedure were trained to press for ICS and two standard intensities of ICS were determined. Across rats, the low ICS ranged from 10 to 22 μA (mean = 16.7 μA) and the high ICS ranged from 12 to 25 μA (mean = 20.0 μA). Once rats' rates of pressing were stable, they began receiving two injections before each day's testing. Across the initial days of each assessment, the rats received only placebos. Subsequent to 3 consecutive days of stable pressing under the influence of placebos, the rats then received COC and the placebo for ISR, daily. Once there were 3 consecutive days of stable and facilitated pressing under the influence of COC, there was a test day, on which both COC and a dose of ISR were given. Across the next 3 days, rats received COC and the placebo for ISR, followed by 3 more days of only placebos.

Upon completion of a test and upon the condition that rates of pressing under placebo did not markedly vary, a rat was assigned another dose of ISR for testing. Each rat experienced all doses of ISR in one of three dose orders. The dose orders were either (a) 1.0, 3.0, and 10.0 mg/kg; (b) 3.0, 10.0, and 1.0 mg/kg; or (c) 10.0, 1.0, and 3.0 mg/kg.

The data consisted of the scores from (a) the 3 days of placebos prior to the first day with COC, (b) the 3 days of COC prior to the test day, (c) the test day, (d) the 3 posttest COC days, and (e) the 3 posttest placebo days. Thus, for each assessment of a dose, there were 13 pairs of scores (number of presses for low and high ICS) for each rat.

Initial analyses revealed that rats' pressing under the influence of placebos was generally stable across all phases of testing. Therefore, to simplify the presentation of the results, the data representing the effects of placebos are the 3-day mean number of presses prior to giving COC.

Similarly, initial analyses revealed that rats' pressing under the influence of COC was generally stable, and greater than rates under only placebos, across all phases of testing. Therefore, to simplify the presentation of the results, the data representing the effects of COC are the means from the 3 days prior to a dose of ISR.

Given these data reductions, the data associated with each test of a dose of ISR conformed to a 3 by 2 ANOVA, having repeated measures, with factors of drug condition (placebo, COC, or COC plus ISR), and intensity of ICS, respectively.

RESULTS

1.0 mg/kg of Isradipine

The data associated with 1.0 mg/kg ISR are shown in Fig. 1A. The ANOVA of those data yields reliable main effects of drug condition, $F(2, 10) = 4.38$, $p = 0.04$, and intensity of ICS, $F(1, 5) = 63.2$, $p = 0.0005$. The interaction term is also a reliable source of variance, $F(2, 10) = 17.3$, $p = 0.04$.

A comparison of scores of placebo vs. COC confirms that COC facilitated pressing, $F(1, 5) = 26.3$, $p = 0.004$. On the other hand, a comparison of scores of placebo vs. COC plus ISR fails to reveal reliable differences, $F(1, 5) = 0.87$, $p = 0.39$. A comparison of scores of COC vs. COC plus ISR fails to reveal a reliable effect of kind drug condition, $F(1, 5) = 3.14$ $p = 0.14$, but the interaction term is a reliable source of variance, $F(1, 5) = 17.8$, $p = 0.008$. A visual inspection of the data leads to the conclusion that 1.0 mg/kg of ISR may have reduced COC's facilitation of pressing at high ICS but not at low ICS. However, *t*-tests, for dependent measures, reveal that scores of COC compared to those of COC plus ISR are neither reliably different at either low ICS, $t(5) = 1.04$, $p = 0.34$, nor at high ICS, $t(5) = 2.40$, $p = 0.06$. In brief, 1.0 mg/kg of ISR appeared to block or attenuate the ability of 5.0 mg/kg of COC to facilitate rats' pressing, but the extent and uniformity of the effect does not meet standards of statistical significance.

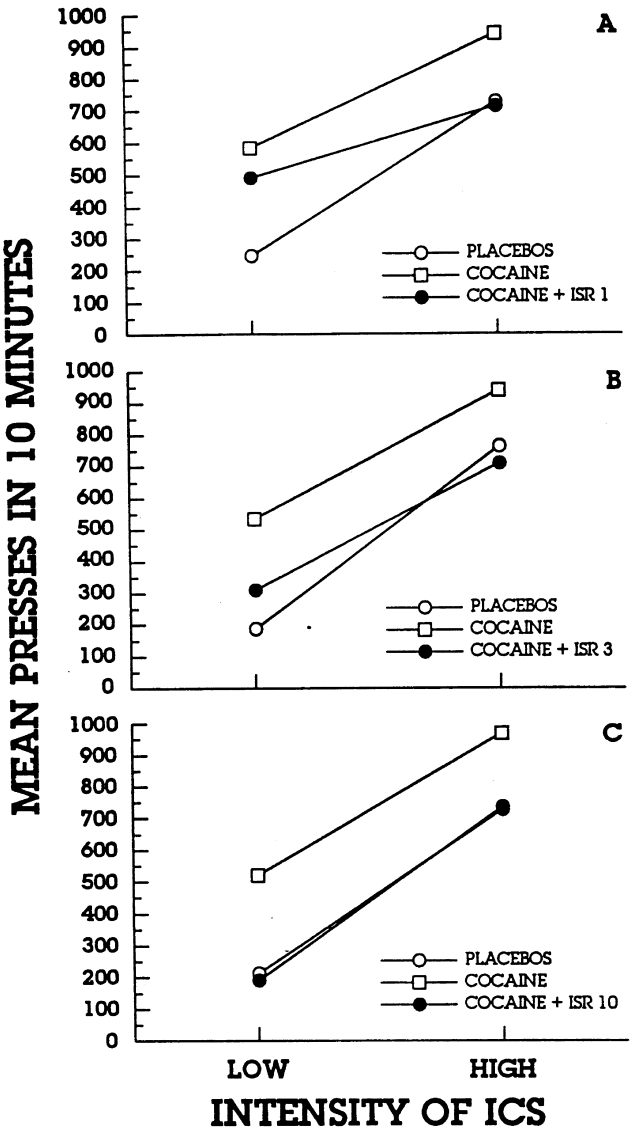

FIG. 1. Summarized in A, B, and C, respectively, are the effects of 1.0, 3.0, and 10.0 mg/kg of isradipine (ISR) on the ability of 5.0 mg/kg of cocaine to facilitate rats' ($n = 6$) pressing for rewarding electrical intracranial stimulation (ICS).

3.0 mg/kg of Isradipine

The data associated with 3.0 mg/kg ISR are summarized in Fig. 1B. The ANOVA of those data yields reliable main effects of drug condition, $F(2, 10) = 5.13$, $p = 0.03$, and intensity of ICS, $F(1, 5) = 25.8$, $p = 0.004$. The interaction term is also a reliable source of variance, $F(2, 10) = 8.23$, $p = 0.008$.

A comparison of the placebo and COC scores confirms that COC facilitated pressing, $F(1, 5) = 16.8$, $p = 0.009$. Under the influence of COC plus ISR, the rats' mean rates of pressing were not reliably different than under placebos, $F(1, 5) = 0.10$, $p = 0.77$. Finally, rats' mean rates of pressing under the influence of COC plus ISR were reliably lower than under COC, $F(1, 5) = 7.08$, $p = 0.04$. In brief, 3.0 mg/kg of ISR blocked the ability of 5.0 mg/kg of COC to facilitate pressing.

10.0 mg/kg of Isradipine

The data associated with 10.0 mg/kg ISR are summarized in Fig. 1C. The ANOVA of those data yields reliable main effects of drug condition, $F(2, 10) = 18.6$, $p = 0.0004$, and intensity of ICS, $F(1, 5) = 38.8$, $p = 0.001$. The F-value for the interaction is $F(2, 10) = 0.28$, $p = 0.76$.

Once again, COC facilitated pressing, $F(1, 5) = 190.6$, $p = 0.00004$. The COC plus ISR scores are not reliably different from the placebo scores, $F(1, 5) = 0.009$, $p = 0.93$. Finally, rats' mean rates of pressing under the influence of COC plus ISR were reliably lower than under COC $F(1, 5) = 19.1$, $p = 0.007$. In brief, 10.0 mg/kg of ISR blocked the ability of 5.0 mg/kg of COC to facilitate pressing.

DISCUSSION

Isradipine dose relatedly attenuated the ability of 5.0 mg/kg COC to facilitate rats' pressing for ICS. At 1.0 mg/kg, ISR appeared to reduce COC's ability to facilitate pressing, but the effects were not uniform. The 3.0 and 10.0 mg/kg doses of ISR completely blocked COC's ability to facilitate rats' pressing for ICS.

Of the six rats in this experiment, two seemed lethargic after the 20-min session on the day when they received 10.0 mg/kg of ISR. Later, on that same day, both appeared to be acting normally. The next day, both rats pressed at their average COC levels, and neither rat lost weight.

EXPERIMENT 2

A potential medicine for the treatment of COC addiction must meet a number of criteria. For example, such a drug should have neither addiction liability, nor should its effects wane with repeated dosing. The potentially therapeutic drug should not produce adverse effects (e.g., physical discomfort, dysphoria) that would threaten compliance with a regimen of its self-administration.

In Experiment 1, 3.0 mg/kg of ISR suppressed COC's ability to facilitate pressing for ICS. Although, this dose did not appear to be debilitating, it might have produced a general, yet unobservable, malaise that could account for the apparent attenuation of COC's facilitation of pressing (14). To assess this possibility, we assessed ISR's effects on pressing for ICS alone. Furthermore, to get additional information, we gave 3.0 mg/kg of ISR on 5 consecutive days. In addition to revealing a potential debilitating effect, this procedure is apt to reveal any addiction liability of ISR, because addiction liability is indexed by a drug's ability to enhance pressing for ICS (9,14).

METHOD

Five rats were prepared and trained as described in the General Method Section. Among these rats, low ICS ranged from 10 to 18 μA (mean = 13.4 μA) and high ICS ranged from 12 to 20 μA (mean = 16.2 μA). Testing spanned 11 days. Across days 1–3 and days 9–11 the rats received placebos. Across days 4–8 rats received 3.0 mg/kg of ISR daily.

RESULTS

The results are presented in Fig. 2. The data of the figure conform to an overall 11 by 2 ANOVA, having repeated mea-

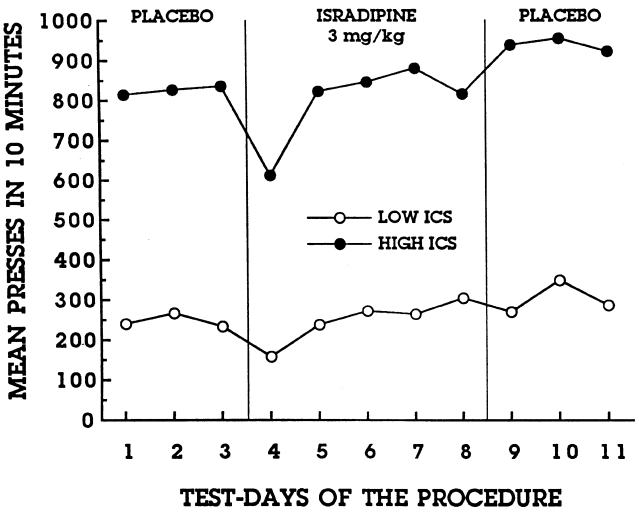

FIG. 2. Depicted are the effects of 3.0 mg/kg of isradipine on rats' (n = 5) pressing for ICs when given before five consecutive daily sessions.

sures, with factors of days and intensity of ICS. As expected, there is a reliable main effect of intensity of ICS, $F(1, 4) = 71.8$, $p = 0.001$ .The ANOVA also reveals a reliable main effect of days, $F(10, 40) = 2.78$, $p = 0.01$. The interaction term is not a reliable source of variance, $F(10, 40) = 1.17$, $p = 0.34$.

Subsequent analyses confirm that rats' mean rates of pressing under the influence of placebo were stable across days, both before and after the 5-day period of administration of ISR. In subsequent analyses, the data representing the effects of placebos are the 3-day mean scores across days 1–3 for each rat.

An ANOVA of the data from the days when ISR was given yields a reliable main effect of days, $F(4, 16) = 8.49$, $p = 0.0007$. Upon inspection of Fig. 2, it is apparent that ISR lowered rats' mean rate of pressing on the first day of its administration. Indeed, an ANOVA of the data associated with last 4 days of ISR fails to reveal a reliable day effect, $F(3, 12) = 0.49$, $p = 0.70$. A comparison of the mean placebo scores with the scores of the first day of ISR reveals that ISR marginally reduced pressing, $F(1, 4) = 6.39$, $p = 0.06$. A similar comparison of the mean placebo scores and the mean scores across the last 4 days of ISR administration fails to reveal a reliable difference between these scores, $F(1, 4) = 0.14$, $p = 0.73$. Finally, a comparison of the data of the 1st day of ISR with the mean score of the last 4 days of ISR reveals a reliable difference between these scores, $F(1, 4) = 25.9$, $p = 0.007$. Given these results, its can be concluded that the reliable day effect of the overall ANOVA of the data is due to reduction in rat's pressing on the first day of administration of ISR.

DISCUSSION

Except for the first day of administration, 3.0 mg/kg of ISR had little, if any, observable effect on rats' pressing for ICS. However, because this dose lowered pressing on the first day of administration, the conclusion that ISR blocked COC's ability to facilitate pressing for ICS (Experiment 1) is tenuous. Accordingly, instead of specifically blocking the reward-relevant effects of COC, ISR may have produced nonspecific effects (e.g., a mild malaise) that interfered with the rats' motivation to press for ICS. Therefore, before concluding that ISR may be useful for treating COC abuse, it is necessary to examine its effect on COC's facilitation of pressing for ICS when given daily.

EXPERIMENT 3

In Experiment 2, 3.0 mg/kg of ISR did not reduce rats' pressing for ICS, except on the first day of administration. It is possible that, in Experiment 1, this dose of ISR produced a nonspecific effect that canceled COC's effect on rats' pressing for ICS, rather than blocking the reward-relevant effects of COC. It follows, that if ISR does not block COC's reward-relevant effects, then the potential for ISR being an effective drug for treating COC addiction is greatly diminished. Therefore, it is important to examine the effects of repeated daily administrations of ISR on COC's reward-relevant effects. In addition, an important criterion for a putative medicine for an addiction to COC (or any other drug) is that the agent's effects do not wane with repeated administrations. Thus, in these procedures, the effects of 3.0 mg/kg of ISR on COC's facilitation of pressing for ICS were tested for 5 consecutive days.

METHOD

Seven rats were prepared and trained as described in the General Methods Section. The doses of COC and ISR used were 5.0 and 3.0 mg/kg, respectively. For these rats, low ICS ranged from 10 to 30 μA (mean = 17.1 μA) and high ICS ranged from 12 to 35 μA (mean = 21.9 μA). Similar to the procedures of Experiment 1, once rats' rates of pressing were stable, they began receiving two injections before each day's testing. Subsequent to 3 consecutive days of stable pressing under the influence of only placebos, the rats received COC and the placebo for ISR, daily. After 3 consecutive days of stable and facilitated pressing under the influence of COC, the rats received both COC and ISR for 5 days. Then, there were 3 days of COC and the placebo for ISR, followed by 3 days of placebos. Thus, there were 17 pairs of scores for each rat.

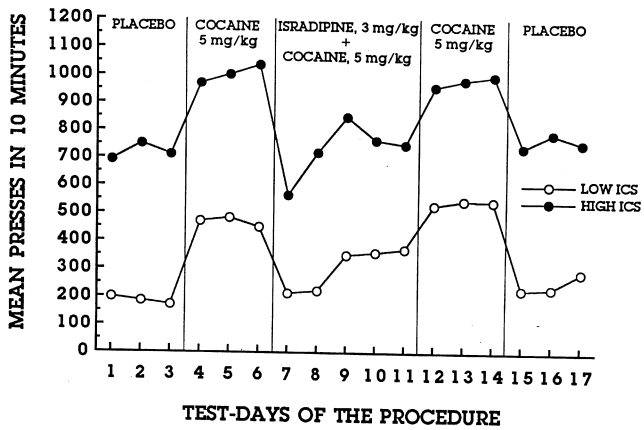

FIG. 3. Depicted are the effects of isradipine on the ability of cocaine to facilitate rats' (n = 7) pressing for ICS across five consecutive daily sessions (days 7–11 of the procedure).

RESULTS AND DISCUSSION

The results are presented in Fig. 3. The data of the figure conform to a 17 by 2 ANOVA, having repeated measures, with factors of days and intensity of ICS. As expected, there are reliable main effects of intensity of ICS, $F(1, 6) = 38.9$, $p = 0.0008$, and days, $F(16, 96) = 4.87$, $p = 0.0000004$. The interaction term is not a reliable source of variance, $F(16, 96) = 0.70$, $p = 0.79$.

As in the previous experiments, analyses of the data when only placebos were given revealed that rats' mean rates of pressing under the influence of only placebos were stable across days, both before and after administration of COC. Further, pressing under placebo did not differ across phases (before and after dosing with COC), suggesting that the intervening procedures did not produce lasting (i.e., carryover) effects. In subsequent analyses, the data representing the effects of placebos are the 3-day mean scores just before the days with COC.

Similarly, initial analyses revealed that rats' rates of pressing under the influence of COC were generally stable, and greater than that seen under only placebos, across all phases of testing. Further, pressing under the effects of COC did not differ across phases (before and after dosing with ISR), suggesting that COC plus ISR did not produce carryover effects. In subsequent analyses, the data representing the effects of COC are the 3-day mean scores just before the days with ISR. It should be noted that, as expected, COC reliably facilitated pressing for ICS, $F(1, 6) = 47.1$, $p = 0.0005$.

Analyses of the data from the 5-day period when COC and ISR were given reveals a reliable source of variance across days of testing, $F(4, 24) = 4.77$, $p = 0.006$. Upon inspection of Fig. 3, it appears that ISR lowered rats' mean rates of pressing more on the first day of administration than on any of the other days, a finding similar to that seen in Experiment 2. An ANOVA of the data from the last 4 days of COC plus ISR fails to reveal reliable differences in rats mean pressing across those days, $F(3, 18) = 2.40$, $p = 0.10$. This suggests that the reliable day effect of the analyses of the entire 5-day period of COC and ISR administration is due to the scores from the first day of that period.

A comparison of the mean scores of COC versus the mean scores from the last 4 days of COC plus ISR confirms that ISR reliably lowered pressing, $F(1, 6) = 7.75$, $p = 0.03$. A similar analysis fails to reveal a reliable difference between the mean placebo and the 4-day mean COC plus ISR scores, $F(1, 6) = 3.26$, $p = 0.12$. In brief, results of these procedures lead to the conclusion that ISR reliably blocks COC's ability to facilitate pressing for ICS across repeated days of administration, without reducing pressing below placebo levels.

Another issue is whether the effects of 3.0 mg/kg of ISR waned with repeated dosing. As depicted in Fig. 3, there is an apparent trend for rats' pressing to increase across days when both COC and ISR were given. However, there was no reliable difference in rats' mean rate of pressing across the last 4 days of administration of ISR. Furthermore, rats' mean pressing for ICS was reliably lower on the last day of COC and ISR compared to their mean pressing under the influence of COC, $F(1, 6) = 7.24$, $p = 0.04$. In summary, the results demonstrate that 3.0 mg/kg of ISR persistently blocked the effects of 5.0 mg/kg of COC across 5 consecutive days of testing.

GENERAL DISCUSSION

Each kind of preclinical test assessing the rewarding effects of drugs has limitations. The test involving pressing for ICS has the limitation of potentially leading to a false conclusion about a drug's rewarding effects because a drug, or a combination of drugs, may merely be affecting activity and ability to press. Consequently, other kinds of assessments are used to check on the conclusions that might be drawn. Here, it is shown that ISR blocks COC's ability to facilitate pressing for ICS. The result suggests that ISR blocks the reward of COC, but confirming evidence is needed. Fortunately, there is other evidence to bring to bear on the issue.

ISR may block COC's effects by affecting motor ability. ISR did not, however, reduce, except on its first administration, pressing for ICS when COC was not given. Additionally, Calcagnetti and Schechter (2) have shown that ISR by itself does not affect locomotor activity, although it does block COC-induced locomotion. So, under the influence of ISR, rats do have the capacity to press a lever at high rates for ICS. Indeed, under the influence of COC plus ISR, the rats clearly press more at high ICS than they do at low ICS when only placebos are given (compare rates of pressing for low ICS under placebos with rates of pressing for high ICS under COC plus ISR in Figs. 1 and 3).

The ideal pharmacological adjunct to other treatments for addiction to COC should neither be toxic nor addicting. There are no reasons to suppose that ISR would be addicting because it did not facilitate pressing for ICS by itself (Experiment 2). ISR does not establish a conditioned place preference or a conditioned place aversion (2). So it is difficult to argue that ISR's ability to block COC's facilitation of pressing for ICS is merely due to a malaise. ISR may merely reduce motivation, in general, and not reduce the motivation induced by COC, but the fact that ISR, by itself, did not reliably modify pressing for ICS, except initially, indicates that ISR does not reduce all motivation.

ISR's first day effects need to be examined further. It is possible that this first day effect may not occur when ISR is given orally to people. Indeed, extensive testing in humans has shown a minimum of side effects associated with CCBs. Reports indicate headaches and dizziness as the most common side effects (1). It may be possible to avoid these side effects by beginning administrations of ISR at lower doses and gradually increasing the dose over days.

COC produces some serious side effects with respect to blood flow in the brain. COC induces constriction of small arteries of the brain and platelet-rich thrombi (18), which lead to occlusion of the small arteries. Consequently, users of COC are likely to suffer from focal cerebral circulatory deficits [e.g., (8,20–22)]. Prior to permanent damage, it is possible that CCBs could be part of a therapy used for restoring some of the lost functioning due to focal circulatory effects (6,7). Although ISR's therapeutic effects have not been directly assessed with respect to COC-induced cerebrovascular deficits, it seems likely that ISR might be beneficial. ISR does affect hypertension and platelet aggregation (1). Given this potentially beneficial side effect and the confirmation that ISR blocks COC's reward-relevant effects, it seems that ISR has considerable promise as a therapeutic agent among persons abusing COC.

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