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Amlodipine, a Calcium Channel Inhibitor, and Cocaine and Ethanol's Reinforcing Effects

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GARDELL, L. R., M. L. REID, C. A. CAVALLARO, S. E. BURGESS, R. F. WALLACE, C. L. HUBBELL AND L. D. REID. *Amlodipine, a calcium channel inhibitor, and cocaine and ethanol's reinforcing effects.* PHARMACOL BIOCHEM BEHAV **64**(3) 567–572, 1999.—The effects of amlodipine (from 0.1 to 3.0 mg/kg) on rats' pressing for rewarding brain stimulation, with and without cocaine administration, were assessed. None of the doses reliably modified the effects of cocaine. Also, amlodipine was given to two groups of rats taking alcohol: one group that was regularly taking a sweetened alcoholic beverage and the other taking an unsweetened alcoholic beverage. The only discernible effects of amlodipine on alcohol intake were associated with the highest dose and only with rats taking the sweetened beverage. The effects of this high dose could easily be attributable to behavioral toxicity elicited by the dose. In contrast, and confirming previous work, isradipine, another calcium channel inhibitor, produced reliable reductions on both cocaine's and alcohol's reinforcing effects. Despite the similarity of isradipine and amlodipine, isradipine apparently has some unique features with respect to cocaine and alcohol. © 1999 Elsevier Science Inc.

Calcium channel inhibitors Amlodipine Isradipine Cocaine Ethanol Medications for alcoholism Medications for cocaine Brain stimulation reward Polydrug abuse

THIS article is an extension of Gonzales et al. (8), a report indicating that isradipine (ISR), a calcium channel inhibitor (CCI), blocks the ability of cocaine to facilitate rats' pressing for intracranial stimulation (ICS), a finding supporting previous work (6,12,13,15). This is also an extension of Gardell et al. (7), a report that ISR significantly reduced rats' intake of alcoholic beverage in circumstances usually sustaining large intakes, a finding supporting previous work (5,20–22). From these and similar observations, it was concluded that ISR by itself, or in combination with naltrexone (3,4,7), might be useful in treating cocaine and alcohol use disorders.

The question arises, however, as to whether ISR is unique or whether any CCI might be just as effective as ISR. Using very similar methods to those used in the studies assessing ISR, amlodipine (AML), another CCI, was tested. AML, like ISR, is an L-type CCI. Both drugs are useful in treating hypertension (1,9). To complement the study of AML, there were additional assessments of ISR.

METHOD

Subjects

The subjects of all procedures were adult, male, Sprague–Dawley rats, purchased from Taconic Farms (Germantown, NY) when they weighed about 225 g. They were individually housed in standard hanging cages in a windowless room, maintained at about 22°C, having 12 h/day incandescent lighting, beginning at 0700 h. Food was always available to all rats in their home cages. For rats of the ICS procedures, water was also always available. For the rats drinking alcohol, fluids were provided daily, but on a schedule.

Drugs

The dose of cocaine HCl (Sigma, St. Louis, MO) was 5.0 mg/kg and was administered intraperitoneally (IP), 15 min before a test session. The vehicle for cocaine was physiological

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saline (0.9% NaCl), and IP injections of vehicle were the placebos for cocaine administration.

The doses of AML (Pfizer) were 0.1, 0.3, 1.0, and 3.0 mg/kg, IP. AML was given 20 min before tests involving cocaine and 30 min before sessions when alcoholic beverages were presented (see below). The vehicle for AML was a solution of 5% dimethyl sulfoxide (DMSO) in deionized water. Injections of vehicle for AML served as the placebo. Note, that in the procedure with alcohol, the effects of the 0.1 mg/kg dose of AML were not assessed.

In the tests involving cocaine, the dose of ISR (Novartis) was 2.0 mg/kg, IP, given 20 min before the session. The vehicle for ISR was 5% polyoxyethylene–sorbitan monooleate (Tween 80) in deionized water, and injections of the vehicle were the placebos for ISR. The 2.0 mg/kg dose had not been tested previously. The dose is between the doses of 1.0 and 3.0 mg/kg, both of which have been tested in assessments with cocaine and pressing for ICS (8,14). The 1.0 mg/kg dose of ISR produced only slight reductions in cocaine's effects, whereas the 3.0 mg/kg blocked cocaine's rate-enhancing effects. In tests involving alcohol, ISR was given in doses of 0.1, 0.3, 1.0, and 3.0 mg/kg, 30 min before testing.

Assessments with AML and Cocaine

To study cocaine's effects, rats were each fixed with a chronically indwelling bipolar electrode so that ICS activated the medial forebrain bundle as it coursed through the lateral hypothalamus. The standard procedures (17) used to implant electrodes involved heavy anesthesia (sodium pentobarbital, 50 mg/kg, IP) and commercially available electrodes insulated except at their cross-section (MS 303/2, Plastics One, Roanoake, VA). The coordinates for the stimulating tips of the electrodes were 3.8 mm posterior to bregma, 1.6 mm lateral to the midline, and 8.6 mm from the top of the skull, with the plane of the skull between bregma and lambda being perpendicular to the electrode shaft.

It was arranged so that each bar press, in a standard operant chamber, delivered 0.3 s of ICS by way of electrode leads allowing free movement of the rat in the chamber. ICS was 60 Hz sine waves of varying intensities, but always less than 40 μA (rms). If a rat pressed the lever during an ICS, the lever press was recorded, but no ICS was delivered as a consequence of that press.

Following recovery from surgery, a rat was trained to press a lever for ICS. During the initial periods with ICS, intensity was varied to select two intensities: one just above the threshold for sustaining pressing, and one sustaining high, but not maximal, rates of pressing. Across subjects, low ICS ranged from 7 to 30 μA (mean = 15.0 μA), and high ICS ranged from 8 to 35 μA (mean = 17.9 μA).

After selection of the intensities, each subject's pressing was measured daily. A daily session was 20 min of four 5-min segments with access to high, low, low, and high ICS, in that order. The mean number of presses made during 10 min at each intensity were the data of each session. The assessments of cocaine, AML, and cocaine plus AML began after rats' rates of pressing were stable across, at least 3 days under placebo and under cocaine.

In accordance with the rationale and procedures described in Pabello et al. (14), each rat was given placebo on 1 day followed by cocaine on the next. This administration of cocaine every other day continued throughout testing. Concurrent with the schedule of cocaine administration, six rats received 2 days of each of the following: 0.0, 1.0, 0.3, and 0.1 mg/kg of AML, in that order, across an 8-day period, with cocaine given on the second, fourth, sixth, and eighth days. Four other rats received a higher dose, 3.0 mg/kg of AML. They were tested across four days and given cocaine on the second and fourth day. On days 3 and 4, they received 3.0 mg/kg of AML. This schedule of dosing allowed an assessment of the effects AML on both pressing for ICS with and without cocaine.

With the completion of the tests with AML, five additional rats were subjected to roughly the same procedure, except a dose of ISR was used instead of AML. The procedure lasted 4 days, and began after subjects had shown stable rates of pressing with no drug and marked enhancement of pressing under the influence of cocaine. On days 2 and 4, rats received cocaine. Days 3 and 4 of the 4-day period, the rats also received ISR, 2.0 mg/kg.

Assessments with AML and Alcohol

Two alcoholic beverages were used. One was 6% ethanol in tap water, i.e., 6 g of ethanol for every 100 g of solution. The other was 12% ethanol in sweetened water, i.e., 12 g of ethanol, 0.25 g saccharin sodium hydrate, and 87.75 g of water for every 100 g. Concurrent with the presentation of either alcoholic beverage, tap water was presented.

Bottles equipped with ball-point sipping tubes were used to present fluids. The differences in weights of the bottles before and after their presentations, corrected for spillage (10), were the data of intakes.

Seventy-two rats were placed on a daily regimen designed to elicit moderately high, stable levels of daily intake of ethanol. The daily regimen involved providing water and the sweetened alcoholic beverage daily for 2 h (during the light portion of daily light–dark cycle). Under this regimen, rats, at first, take little ethanol but eventually take, on average, over 2.0 g/kg of ethanol a daily session (10,11,16,18). Across the initial 2 months on the daily regimen, it was suspended twice for a period of either 10 or 20 days, during which time rats had food and water always available, but no alcoholic beverage. Following this initial period, there was a month on the daily regimen. Then, the alcoholic beverage was changed, in stages until the beverage was the 6% unsweetened beverage. After another period of intakes and a period of no opportunity to take alcohol, half of the rats were again presented with the sweetened beverage. After this change, the rats continued on the daily regimen for 25 days before an assessment of effects of AML. The consequences of this history of daily intakes of alcoholic beverage was (a) one group with stable intakes of sweetened alcoholic beverage, and (b) one with stable intakes of unsweetened alcoholic beverage.

On the first day of the assessment, all the rats received placebos. Then, four groups (n = 9) of those getting the sweetened beverage were selected so that their mean intakes of ethanol (g/kg) was roughly the same. One of four doses of AML (0.0, 0.3, 1.0, or 3.0 mg/kg, IP, 30 min before presentation of fluids) was randomly assigned to be given to a group. The rats getting unsweetened solution were treated in the same way.

To assess ISR, another group was used (n = 35). These rats had a similar history of extensive opportunities to take the sweetened alcoholic beverage (i.e., daily opportunities on the same daily regimen with brief, periodic periods of no opportunity to take alcohol) except that they had not been subjected to the change in alcoholic beverage. Before these tests, subjects had 50 days on the 2-h daily regimen of limited access to water and alcoholic beverage. On the first day of the test, all rats were given placebos. On the next day, rats were randomly

assigned to receive either 0.0, 0.1, 0.3, 1.0, or 3.0 mg/kg of ISR ($n = 7$ per dose).

RESULTS

Assessments with AML and Cocaine

The results using doses of 1.0 mg/kg and less of AML are presented in Fig. 1. Those data conform to a 4 × 2 × 2 analysis of variance (ANOVA), having repeated measures, with factors of dose of AML, saline vs. cocaine, and intensity of ICS, respectively. As expected, cocaine reliably facilitated pressing for ICS, $F(1, 5) = 15.9$, $p = 0.01$, and pressing for high ICS was reliably greater than for low ICS, $F(1, 5) = 64.2$, $p = 0.0005$. No other reliable sources of variance are revealed by the ANOVA. A 4 × 2 ANOVA having repeated measures, with factors of dose of AML and intensity of ICS, respectively, of data associated with the days on which saline was given reveals that AML did not reliably affect pressing for ICS, $F(3, 15) = 1.33$, $p = 0.30$. A similar ANOVA reveals that AML did not affect pressing on the days with cocaine, $F(3, 15) = 0.89$, $p = 0.47$. Notice that cocaine clearly enhanced pressing when rats received 0.3 and 0.1 mg/kg of AML. Notice, also, that the dose of 1.0 mg/kg seemed to reduce cocaine's ability to enhance pressing, but the extent of the reduction was not sufficient to meet standards for statistical significance.

Given the results presented in Fig. 1, we assessed the effects of 3.0 mg/kg of AML and the results of that assessment appear in Fig. 2. The ANOVA of those data reveals that, as expected, cocaine reliably facilitated pressing for ICS, $F(1, 3) = 50.4$, $p = 0.006$, and that rats press more for high than low ICS, $F(1, 3) = 15.7$, $p = 0.03$. No other reliable sources of variance are revealed by the ANOVA. In brief, this dose of AML neither affected pressing for ICS nor did it affect cocaine's ability to facilitate pressing.

Figure 3 presents the results with ISR and cocaine. The overall 2 × 2 × 2 ANOVA, having repeated measures, with factors associated with injections of ISR injections of cocaine, and intensity of ICS, respectively, reveals that ISR reliably reduced pressing, cocaine reliably increased pressing, and that, once again, rats press more for high than low ICS (all ps $<$ 0.02). The ANOVA also revealed a reliable interaction be-

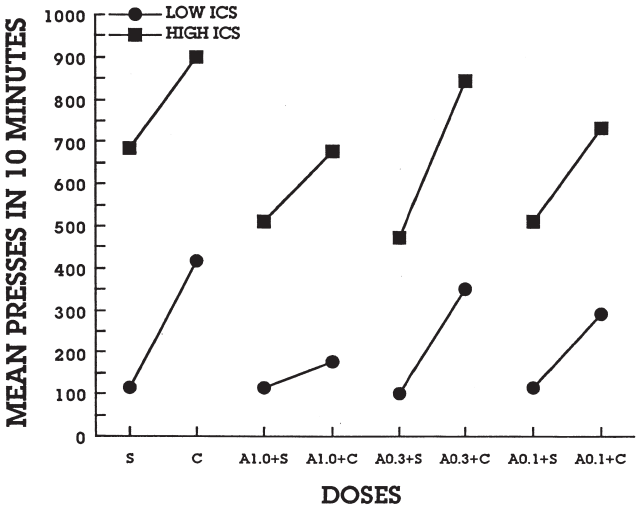

FIG. 1. The effects of amlodipine (A) on the ability of cocaine to facilitate pressing for ICS. The data reflect 8 consecutive days of testing ($n = 6$). S and C denote days on which saline or cocaine (5 mg/kg) were administered. Notice that each dose of AML (in terms of mg/kg) was tested first with saline and then, on the next day, with cocaine. Also notice that the effects of saline and cocaine by themselves are presented and that cocaine facilitates pressing for ICS. None of the doses of AML affected pressing for ICS (note the data points associated with saline injections). Furthermore, none of the doses of AML reliably affected cocaine's ability to facilitate pressing.

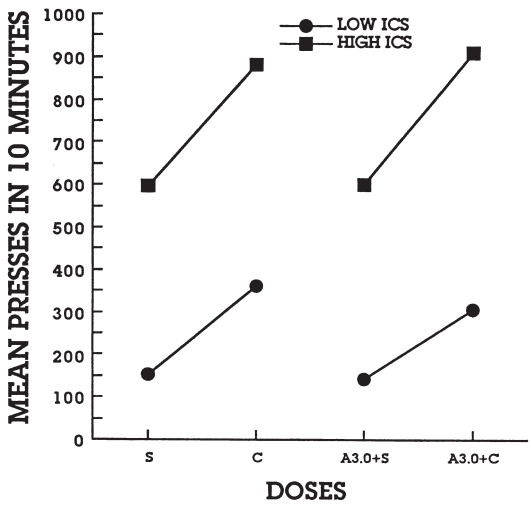

FIG. 2. Depicted are the effects of 3.0 mg/kg of amlodipine (A) on the ability of cocaine to facilitate pressing for ICS. The data reflect 4 consecutive days of testing ($n = 4$). S and C denote days on which saline or cocaine (5 mg/kg) were administered. In brief, this dose of AML neither affected pressing for ICS nor did it affect cocaine's ability to facilitate pressing.

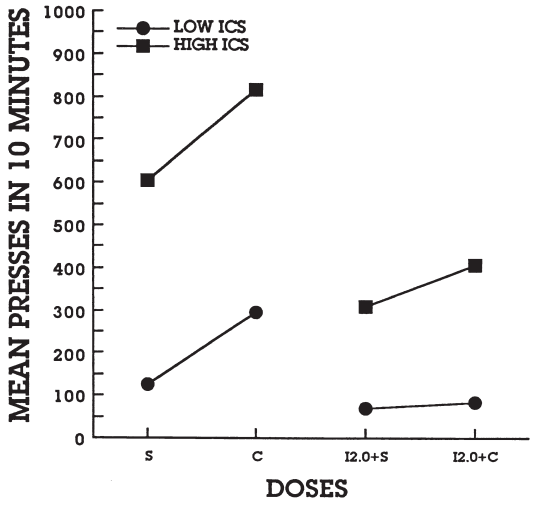

FIG. 3. Depicted are the effects of 2.0 mg/kg of isradipine (I) on the ability of cocaine to facilitate pressing for ICS. The data reflect 4 consecutive days of testing ($n = 5$). S and C denote days on which saline or cocaine (5 mg/kg) were administered. As expected, this dose of ISR reduced pressing for ICS and blocked cocaine's ability to facilitate pressing.

tween the factors of injections of ISR and intensity of ICS, $F(1, 4) = 25.7, p = 0.007$. The interaction between the factors of injections of ISR and injections of cocaine was marginal, but did not meet standards of statistical significance, $F(1, 4) = 5.62, p = 0.08$. These results call for further analyses of specific subsets of the data.

Considering the data of the first two days of the procedure, a 2 × 2 ANOVA reveals that, as expected, cocaine increased pressing for ICS, $F(1, 4) = 14.7, p = 0.02$, and pressing was greater for high ICS, $F(1, 4) = 33.2, p = 0.005$. The interaction was not a reliable source of variance. So, as expected, cocaine reliably increases pressing at both intensities.

A similar analysis was performed with the data of two days with ISR. Intensity was again a reliable source of variance ($p = 0.007$). The effect associated with placebo vs. cocaine yielded an $F(1,4) = 2.41, p = 0.20$, and the interaction was not reliable. Thus, ISR blocked cocaine's ability to facilitate pressing for ICS.

Another ANOVA reveals that ISR, as expected from previous tests, reduced pressing when no cocaine was given, $F(1, 4) = 12.3, p = 0.02$. When ISR is given day after day, however, this initial effect is not seen (8,14). ISR clearly prevented cocaine from enhancing pressing. The ability to block cocaine's effects persist when ISR is given day after day (8,14). The comparison of the scores of day 2 and 4 (cocaine and no ISR; cocaine and ISR) by *t*-tests for dependent groups yields for low ICS, a $t(4) = 2.64, p = 0.06$; and for high ICS, a $t(4) = 6.14, p = 0.004$. In brief, there was a marked difference in reactivity to ISR compared to AML (compare Figs. 2 and 3).

Assessments with AML and Alcohol

In the assessment involving intake of alcoholic beverages, there was no indication that the doses of AML reliably modified rats' intake of water. The findings with respect to intake of ethanol are presented in Figs. 4 and 5. Statistical analyses provide no basis for concluding that the doses reliably modified intakes of the unsweetened alcoholic beverage (Fig. 4). Analyses also provides no basis for concluding that doses of 0.3 and 1.0 reliably reduced intake of the sweetened alcoholic beverage (Fig. 5). The 3.0 mg/kg dose of AML slightly reduced mean g/kg intakes of ethanol among the rats getting the sweetened alcoholic beverage, but the effect only approached standards of statistical significance, $t(8) = 2.23, p = 0.056$.

The relatively slight reduction in intake of the sweetened alcoholic beverage, however, should not lead to the conclusion that high doses of AML might meet standards for being useful in treating alcohol use disorders. Every rat getting this dose showed signs of distress (such as lying flat on the floor of the cage when they are usually aroused by the prospect of getting fluids). This apparent distress was of relatively short duration (lasting about 15 min) and, therefore, did not interfere with intake of water, the unsweetened alcoholic bev-

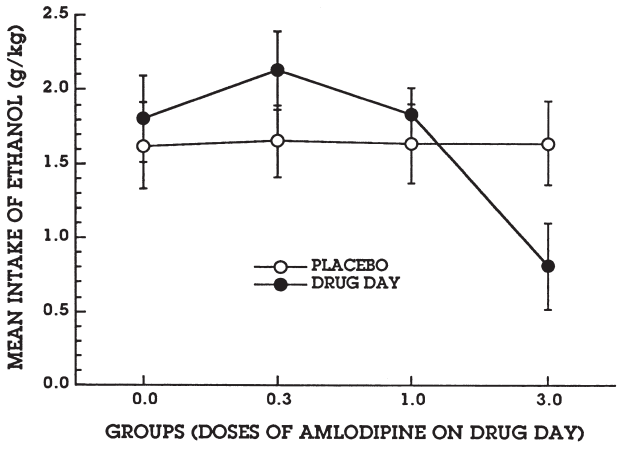

FIG. 5. The effects of AML on rats' mean g/kg intakes of ethanol from a sweetened alcoholic beverage among four groups ($n = 9$) of rats are depicted. These procedures were identical to those of Fig. 4, except that a sweetened alcoholic beverage was used. In brief, none of the doses of AML reliably affected intake of the sweetened alcoholic beverage. Error bars are standard errors of the means.

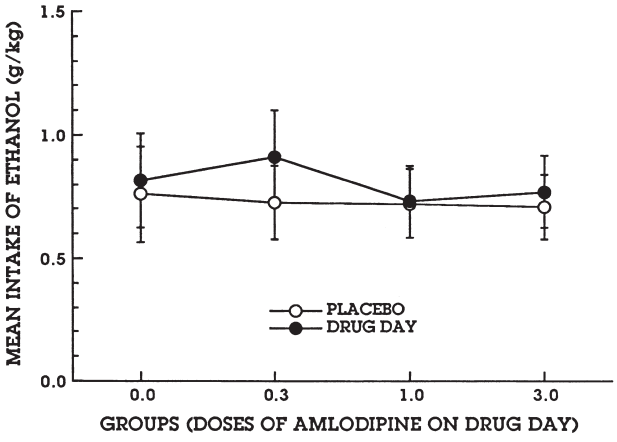

FIG. 4. The effects of AML on rats' mean g/kg intakes of ethanol from an unsweetened alcoholic beverage among four groups ($n = 9$) of rats are depicted. Testing spanned a 2-day period. On the first day, all rats received injections of placebo. On the next day, rats received their respective doses of AML (in terms of mg/kg; drug day). In brief, none of the doses of AML reliably affected intake of the unsweetened alcoholic beverage. Error bars are standard errors of the means.

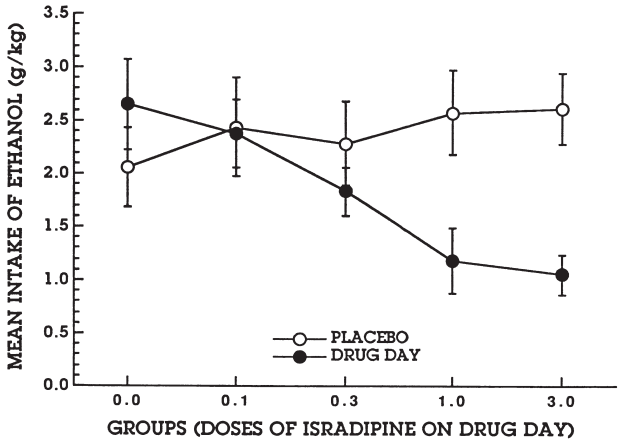

FIG. 6. The effects of ISR on rats mean g/kg intakes of ethanol from a sweetened alcoholic beverage among four groups (n = 7) of rats are depicted. These procedures were similar to those in Figs. 4 and 5. The 1.0 and 3.0 mg/kg doses of ISR reliably reduce rat's mean g/kg intakes of ethanol. Error bars are standard errors of the means.

erage or pressing for ICS in the first procedure. Nevertheless, these signs indicated that it was not useful to test larger doses of AML.

The effects of doses of ISR on intake of alcoholic beverage are summarized in Fig. 6. With those data, a 5×2 ANOVA, having repeated measures, yields a reliable interaction term, $F(4, 30) = 7.97$, $p = 0.0002$, indicating a differential effect of doses. Further assessments indicate that the doses of 1.0 and 3.0 mg/kg reliably reduced intakes, whereas the other doses did not. The values for dependent *t*-tests comparing scores under placebo to those under ISR for 1.0 and 3.0 mg/kg are, respectively, $t(6) = 4.49$, $p = 0.004$ and $t(6) = 4.01$, $p = 0.007$. Although there are indications that an initial dose of ISR produces some hypotension that is manifested behaviorally as reduced activity, the doses of ISR did not produce the marked effects seen with 3.0 mg/kg of AML.

DISCUSSION

ISR meets the standard for being a putative medicine for treating cocaine use disorder by (a) having minimal effects of pressing for ICS by itself, and (b) by blocking the addictive-salient effects of cocaine (8,14). The data presented here are concordant with conclusions drawn from previous studies assessing cocaine under ISR (6,12,13,15). Although initial administrations of ISR do modify pressing for ICS without cocaine, it is well tolerated at doses that block cocaine's ability to enhance pressing for ICS. These data indicate that AML, at the doses tested, has minimal effects on pressing for ICS and on cocaine's ability to enhance pressing for ICS.

ISR dose relatedly reduced rats' intake of alcoholic beverage under circumstances that ordinarily sustain high levels of intake, confirming previous work (2,5,7,20–22). AML did not reduce rats' intake of fluids, except at the highest dose, which reduced intake of sweetened alcoholic beverage.

Generally, rats do not take large amounts of alcohol when they are sick or distressed. We presume that the reduction in intake of alcohol at the high dose of AML was a reaction to the behavioral toxicity seen with this high dose, and not due to AML limiting the reinforcing properties of alcoholic beverages. This presumption is supported by the observation that the rats appeared distressed by the effects of AML, and by the observation of no reduction in intakes with the unsweetened solution. The rats on the sweetened alcoholic beverage probably reduced their intakes more than the others because they ordinarily took larger amounts of alcohol, and that larger amount has a toxicity that could interact with large-dose AML toxicity.

Larger doses of AML may reduce the reinforcing effects of cocaine and ethanol. The 3.0 mg/kg dose, however, clearly produced some signs of distress. So, we probably tested the largest dose of a potentially useful range of doses. Given that the upper limit of the appropriate dose range is 3.0 mg/kg or less, there was little evidence to support the conclusion that AML acted as ISR with respect to alcohol and cocaine's effects. Also, the observations that the 3.0 mg/kg dose of AML produced a marked behavioral effect indicates that the lack of effects seen with AML was not due to the fact that the drug effects were not extant during testing. The drug was producing effects at testing; they were just not effects that were particularly reactive with ethanol or cocaine.

The conclusion of no reliable effects, except some toxic effects at large doses, is subject to the same limitations as any conclusion of null effects. The procedures, however, are nearly the same as those that index reliable effects of ISR and other psychoactive drugs (e.g., opioids and serotonergic drugs).

Using monkeys and a cocaine self-administration procedure, Schindler et al. (23) assessed the effects of three CCIs (diltiazem, nimodipine, and verapamil). They concluded that CCIs did not significantly blunt cocaine reinforcement. The data of Gonzales et al. (8) as well as other data (6,12,13,15), however, indicate the ISR blocks cocaine's reinforcement. From these limited assessments, it appears that ISR has some unique features with respect to cocaine's effects.

Rezvani et al. (22) assessed the effects of the CCIs, diltiazem, nimodipine, and nicardipine on rat's intake of alcoholic beverage. They concluded that the agents were not effective in reducing rats' intakes of ethanol. Their findings plus the results reported here lead to the conclusion that ISR is unique in its ability to reduce rats' intake of alcoholic beverages.

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