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COMPARISON OF FIXED-RATIO AND PROGRESSIVE-RATIO SCHEDULES OF MAINTENANCE OF STIMULANT DRUG-REINFORCED RESPONDING

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SUMMARY

The effectiveness of doses of i.v. cocaine and nomifensine in maintaining lever-press responding in rhesus monkeys was evaluated under two schedules, fixed- and progressive-ratio (FR, PR). The doses that maintained maximum rates of responding under the fixed-ratio schedule were 0.32 mg/kg per injection cocaine and 0.10 mg/kg per injection nomifensine. The fixed-ratio rates maintained by this dose of nomifensine were slightly lower than those maintained by cocaine. Under the progressive-ratio schedule, the maximum response rates developed with 0.32 mg/kg per injection cocaine and 0.32 mg/kg per injection nomifensine. Maximum performances under the progressive ratio were slightly higher with cocaine than with nomifensine. Taken in conjunction with existing data for other drugs and conditions, these data indicate that progressive-ratio schedules may yield information on the relative reinforcing effects of drugs that differs only slightly from that obtained with fixed-ratio schedules.

Key words: Reinforcing effects of drugs — Fixed-ratio schedules — Progressive-ratio schedule — Cocaine — Nomifensine — Rhesus monkey — Schedule of reinforcement

INTRODUCTION

While it is relatively easy to determine whether a specific stimulus is a positive reinforcer or not, a more extensive and different set of procedures is used to determine the relative reinforcing efficacy of different stimuli or different amounts of the same stimulus. One procedure for measuring relative reinforcing strength is the PR schedule. Here, the number of responses neces-

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sary to present the reinforcer is increased systematically until a significant reduction in rate of responding occurs. The response requirement that culminates in a low rate of responding is referred to as a 'breaking point' and is thought to reflect the strength of the reinforcing stimulus. In addition to suggesting the use of this schedule, Hodos [1] demonstrated in rats working on a PR schedule for milk reinforcement, that increased food deprivation led to higher breaking points. Increasing the volume of milk presented as a reward also led to increases in the breaking point, up to a certain volume. With higher volumes, a decrement in the breaking point was observed, probably due to a satiation effect [2].

Progressive-ratio schedules have been used frequently to study the relative reinforcing strengths of intravenously delivered drugs. This is particularly important in view of the interest in developing evaluation procedures for abuse liability of various psychoactive drugs. Griffiths et al. [3] compared the ability of cocaine and three anorectic agents to maintain PR behavior when administered i.v. in a wide range of doses to baboons. These investigators found that the maximally effective dose of the different drugs maintained different breaking points (cocaine > diethylpropion > chlorphentermine > fenfluramine). Progressive-ratio studies have also been made of narcotic drugs. Hoffmeister [4], studied the ability of a range of doses of heroin, codeine, dextropropoxyphene and pentazocine to maintain behavior on PR schedules. Heroin maintained a slightly higher breaking point than codeine, while codeine and dextropropoxyphene maintained similar breaking points which were slightly higher than that maintained by pentazocine. These determinations of a single breaking point as described above take considerable periods of time. For example, Griffiths et al. [5], increased the ratio on a daily basis and, in some cases, a single breaking point determination took 6 days.

Other investigators have compared abuse liability of drugs in experimental studies using the rate of responding on fixed-ratio schedules as the dependent measure [6]. This is perhaps a less complex procedure, and can usually generate information more quickly than the progressive-ratio schedules used to date. The procedure does differentiate among morphine-like drugs. In our laboratory, for example, we have observed that codeine, morphine and methadone [7] maintain relatively higher rates of responding than nalbuphine [8].

Direct comparisons between the ability of FR and PR schedules to indicate the relative reinforcing effects of drugs are rare. Griffiths et al. [5], studied the ability of cocaine, in a range of doses, to maintain responding on PR and FR schedules. They found little difference in the shape of the dose-effect curve, or the dose that maintained maximal behavior, either FR rate or PR breaking point. They concluded that these two procedures, although methodologically distinct, produced quite similar results.

In the present study, a similar comparison was made between PR and FR schedules using two drugs, cocaine and nomifensine. The schedules had markedly different parameters than those used by Griffiths et al. [5]. Those

investigators used a FR value of 160 with a post-injection time out period of 3 h. Their PR schedule started at 160 and doubled every 24 h as long as behavior was maintained above criterion levels. Again, the time out after each injection was 3 h. A much shorter procedure was used in the current study in an attempt to demonstrate that PR studies can be done fairly rapidly. A similar objective prompted an earlier study [9]. Determinations of the rate-maintaining effects of a given dose of a drug under study with the FR procedure could be made in a 2-h session. With the PR procedure, a single session of less than 8 h was usually sufficient to provide information on the breaking point engendered by a specific dose.

Thus, the objectives of the study were to compare the PR and FR performances maintained by cocaine under similar conditions, but conditions that were somewhat different from those in the literature. A second objective was to compare another drug, nomifensine, to cocaine under both schedules. This would provide a systematic replication of the cocaine-dose relations under the two schedules. We had noted earlier that nomifensine maintained self-injection responding in rhesus monkeys [10]. Subsequently, a similar study in rodents appeared [11]. A quantitative comparison of nomifensine to cocaine was of interest under the two schedules.

METHODS

Three male rhesus monkeys served as subjects in this experiment. They were housed in cages with open fronts, and were restrained in these cages by tubular metal harnesses and jointed restraining arms. The restraining harness protected the catheter from the monkey. This harness and arm apparatus allowed the monkeys relatively free movement within the cages [12]. The cages were equipped with two levers and three stimulus lights [6].

Under ketamine and pentobarbital anesthesia, silastic catheters (i.p. 0.08 cm, o.d. 0.24 cm, Rodhelm Reiss Co. Belle Mead, NJ, U.S.A.) were surgically placed in one of either the jugular or femoral veins of the monkeys. These veins were catheterized sequentially as catheters became dislodged from previous sites. The catheter was routed subcutaneously from the site of insertion to the midscapular region where it exited from beneath the skin. At this location, the catheter was joined to a similar catheter that passed through the restraining arm to the outside of the cage. Here it was connected to a roller pump (Model MHRK 55, Watson and Marlow Co., Falmouth, U.K.) that could be operated remotely.

There were two sessions each day, the first starting around 1000 h and lasting no more than 130 min, the second starting around 1600 h and lasting for an indefinite period. In general, when a session began, a red stimulus light came on in the cage. Responses on the lever in the presence of the red light resulted in an infusion of 0.32 mg/kg cocaine. During the infusion, the red light was turned off, and a green light was illuminated. Both lights were off after the injection for a specified length of time, and during this time responses

had no programmed consequence. At the end of this time-out period, the red light was illuminated again, and the cycle was repeated.

When the monkeys were being trained to make the response, the response requirement was set at 1 and gradually increased to 30. Likewise, the post-injection time out (TO) was initially just a few seconds, and gradually increased to 10 min. Once the monkeys were responding under the conditions of the FR 30 TO 10-min schedule at rates in excess of 1 response/s in the presence of the red light, the progressive-ratio schedule was initiated in the afternoon sessions. In the PR schedule, the first drug infusion was given following 30 responses and was followed by a 10-min TO. The second infusion was given following 60 responses, the third after 90 responses and so on in increments of 30. Each injection was followed by a 10-min TO. The maximum number of infusions possible during the session was 30, making the maximum response requirement 900; thus the session terminated after 30 infusions or if no more than two responses were made during a 15-min period with the red light on. The last completed fixed-ratio value was designated as the breaking point.

The regular FR 30 TO 10-min schedule continued in the morning session. Here, the session terminated after 13 infusions or 130 min. When responding was stable in both the morning (FR 30 TO 10 min) and afternoon (PR 30 TO 10 min) sessions, a change was made in the dose of cocaine during a single session, morning or afternoon. The baseline dose was then returned for two or three sessions, and then another dose change was made. Typically, a series of dose substitutions was made first in the FR sessions, and then in the PR sessions. Following completion of the series of cocaine-dose substitutions, similar substitutions were made with a series of nomifensine doses.

In the PR schedule, each dose of cocaine was substituted twice in each monkey. With the FR schedule, various doses of cocaine were substituted only once in each monkey since comparative data are already available for cocaine on FR schedules. With nomifensine, under both schedule conditions, each dose was substituted twice.

The experiments were controlled by a PDP/8e computer (Digital Equipment Corp., Maynard, MA, U.S.A.). The interface and software (SKED) were obtained from State Systems, Inc., Kalamazoo, MI, U.S.A.). The computer and cumulative recording equipment were located in a room adjacent to the monkey test facility, where a closed circuit TV was also available.

RESULTS

Nomifensine and cocaine maintained self-injection behavior on an FR 30 TO 10-min schedule as shown in Fig. 1. The dose-effect curves for the two drugs were quite similar. They took the form of inverted U-shaped functions that are frequently reported with drugs that maintain self-administration behavior. The primary difference was in the potency of the two compounds. Cocaine maintained a peak rate of responding of 3.75 responses/s at 0.32 mg/

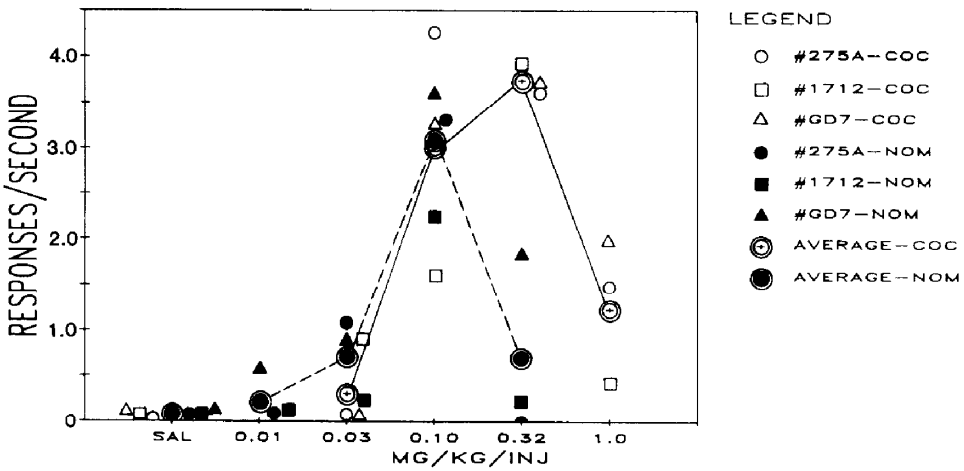

Fig. 1. Rates of FR responding with doses of cocaine nomifensine or saline (SAL). The legend at the right side of the figure gives the codes for the individual monkey data as well as the averaged data for each drug.

kg per injection. Nomifensine maintained a peak rate of responding at 3.06 responses/s at a dose of 0.10 mg/kg per injection. Nomifensine thus was ½ log unit more potent than cocaine in the FR procedure.

Although no time limit was set on the PR session, the monkeys usually responded at high rates or responded very little; thus sessions never lasted longer than 7 h. With the PR schedule, both cocaine and nomifensine maintained maximum breaking points at a dose of 0.32 mg/kg per injection. A higher dose of nomifensine was not tested because the drug is difficult to dis-

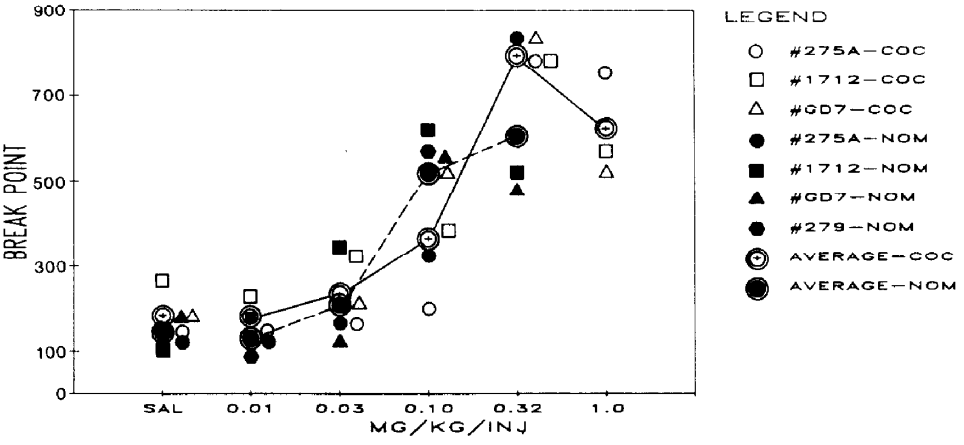

Fig. 2. Breaking points for responding maintained by saline (SAL), nomifensine or cocaine. The legend at the right side of the figure gives the codes for the individual monkey data as well as the averaged data for each drug. Doc, compsimpratio; disk, gdw.

solve in water at the concentrations that would have been necessary to test this dose. It is likely that the breaking point at 1.0 mg/kg per injection nomifensine would have been decreased relative to that at 0.32 mg/kg per injection since two of the three monkeys showed slight decreases in breaking point from 0.10 to 0.32 mg/kg per injection. The fact that average rates increased over this dose range is due to one monkey who had quite a low breaking point at the 0.10 mg/kg per injection dose, and a very high breaking point at the 0.32 mg/kg per injection dose.

DISCUSSION

Both cocaine and nomifensine maintained self-injection responding under both schedules of drug delivery. The doses of drug were strong determinants of result with both schedules. With the FR schedule, the highest doses of both nomifensine and cocaine maintained less rapid rates, sometimes dramatically less rapid rates, than the lower doses. This has been interpreted, not as a decrease in the reinforcing effect of the higher doses, but as a direct effect of the drug on self-injection responding. This direct effect can be lessened by increasing the amount of time between available infusions; thus, high rates of responding are maintained at even higher doses [5].

The PR dose-effect curve for cocaine duplicated closely the FR dose-effect curve. The breaking points did not rise quite as rapidly with increasing doses as did the FR rates, and the decrease in rates at the highest dose was not as profound. This difference in result for the two schedules may have been produced by the larger increases in inter-injection times associated with the progressive-ratio schedule. The same dose (0.32 mg/kg per injection) maintained the maximum rates under both conditions. This result confirms data of Griffiths et al. [5] using much longer procedures with both the FR and PR procedures.

With nomifensine however, rates continued to increase across the tested doses in the PR procedure, even though a decrease in rates was observed in the highest dose under the FR procedure. In this respect, the data with nomifensine are similar to those of Griffiths et al. [3]. They noted a more dramatic reduction in breaking points at high doses with diethylpropion and chlorphentermine than with cocaine and attributed this effect to the much shorter duration of action of cocaine than the other stimulants. Thus, during the 3-h TO following each drug infusion in the Griffiths' et al. study, the cocaine effects may have dissipated more completely than those of diethylpropion or chlorphentermine. In a subsequent study, using higher doses of cocaine, a more convincing reduction in breaking points was demonstrated [5]. If nomifensine is a short-acting drug, it might be possible to explain the lack of downturn at the highest dose under the PR condition by the fact that the PR schedule typically allows more time between drug infusions, thus giving the drug more opportunity to be inactivated, and reducing the direct rate-reducing effects of the drug on subsequent opportunities to respond. Data on the

pharmacokinetics of nomifensine indicate that it does have a short half life (approx. 2 h following oral administration), but that the EEG effects of the drug persist for several hours after it has been cleared from the blood. A metabolite of nomifensine was inactive and short-lived as well and cannot account for this peculiar prolonged effect [13]. Thus, the reason why nomifensine does not show a decreased breaking point is unclear but, consistent with the interpretation of others, may reflect a relative short duration of action or less strong direct effects. Nevertheless, taken together, the two schedules, with both cocaine and nomifensine, produced similar effects. It would appear, under these circumstances, that PR and FR schedules may be controlled by similar processes. When apparent differences occur with the two schedules, it may be that widely different scheduled-controlled histories or temporal differences in controlling factors (e.g. dissipation of direct effects of self-injected drug) are contributing to these differences in result.

These data indicate that FR schedules may provide data on the relative reinforcing effects of drugs that are not markedly different from those obtained with a PR schedule. They also indicate that stable measures of PR breaking points can be obtained relatively rapidly, in a matter of hours rather than over the course of days as has been previously described. This evaluation of PR and FR schedules of reinforcement could be extended to a variety of compounds with different profiles and presumably different reinforcing strengths. This could enhance the generality of our findings of little difference between the two schedules.

Studies in normal humans indicate that a single 100-mg dose of nomifensine, given orally, did not produce euphoria or subjective effects that are in any way different from those following placebo. In the same subjects, 15 mg amphetamine produced marked mood elevation [13]. These data, plus the fact that no abuse problems have arisen with nomifensine over several years of clinical use in Europe, stand in interesting opposition to the data in animals showing the strong reinforcing effects of this drug, comparable in efficacy to cocaine. Although the differences may lie in the route of administration, with less reinforcing capacity present in the orally administered compound, the rapid onset of action following oral dosing suggests that this may not be the entire answer. The data presented here indicate that nomifensine, should it become available in the United States, should be monitored very carefully for instances of abuse. Also, further research with this compound is certainly called for to help in the interpretation of discrepancies between human and animal experimental results.

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