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BRIEF COMMUNICATION

The Discriminative Stimulus Properties of Cocaine and *d*-Amphetamine: The Effects of Three Routes of Administration[1]

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GARZA, R DE LA AND C E JOHANSON *The discriminative stimulus properties of cocaine and* d-*amphetamine The effects of three routes of administration* PHARMACOL BIOCHEM BEHAV 24(3) 765–768, 1986 —Five rhesus monkeys were trained to discriminate intramuscular cocaine (0 25 mg/kg, 10 min presession) from saline In subsequent tests, intramuscular cocaine (0 03–0 5 mg/kg, 10 min presession) and intravenous cocaine (0 03–0 25 mg/kg, 10 min presession) controlled cocaine-appropriate responding in a dose-dependent manner and all monkeys tested reached training criterion (greater than 90% cocaine-appropriate responses) levels after the higher doses were tested *d*-Amphetamine (0 03–0 5 mg/kg) delivered intramuscularly (10 min presession) or intragastrically (60 min presession) also controlled cocaine-appropriate responding in a dose-dependent manner and, at the higher doses, all monkeys tested reached criterion Regardless of route, cocaine and *d*-amphetamine were similar in potency Intragastric cocaine (0 5–16 0 mg/kg, 60 min presession) also controlled cocaine-appropriate responding at some dose in each monkey tested, but the drug was less potent More importantly, the effects of IG cocaine were less systematic possibly due to uncontrolled pharmacokinetic factors

Cocaine *d*-Amphetamine Drug discrimination Routes of administration Rhesus monkeys

IN drug discrimination procedures, reinforcement is made contingent upon one type of operant response in the presence of a drug and another type of response in the presence of its vehicle Under test conditions, doses lower than the training dose typically result in proportional decreases in drug-appropriate responding, i e , a dose-effect function is obtained Furthermore, when drugs other than the training drug are tested, they produce drug-appropriate responding to the extent that they resemble the training drug, i e , there is drug class specificity Drug discrimination procedures can also be used to compare the effects of the same drug or related drugs administered by different routes Such comparisons may be useful for evaluating a drug such as cocaine which presumably has relatively minor effects when given orally [4], or amphetamine which is used therapeutically by the oral route, but is often abused parenterally

Cocaine can function as a discriminative stimulus in primates Although this effect has been shown to be pharmacologically specific [1, 3, 6], little or no information is available on the discriminative stimulus effects of cocaine administered by various routes Downs *et al* [2] reported that in rhesus monkeys orally administered cocaine was 16 times less potent than intramuscular (IM) and intravenous (IV) cocaine on schedule-controlled behavior *d*-Amphetamine given IM and orally, on the other hand, did not differ in potency under the same conditions [2] The purpose of the present experiment was to further compare cocaine and *d*-amphetamine, given intragastrically (IG) and parenterally, on the basis of their

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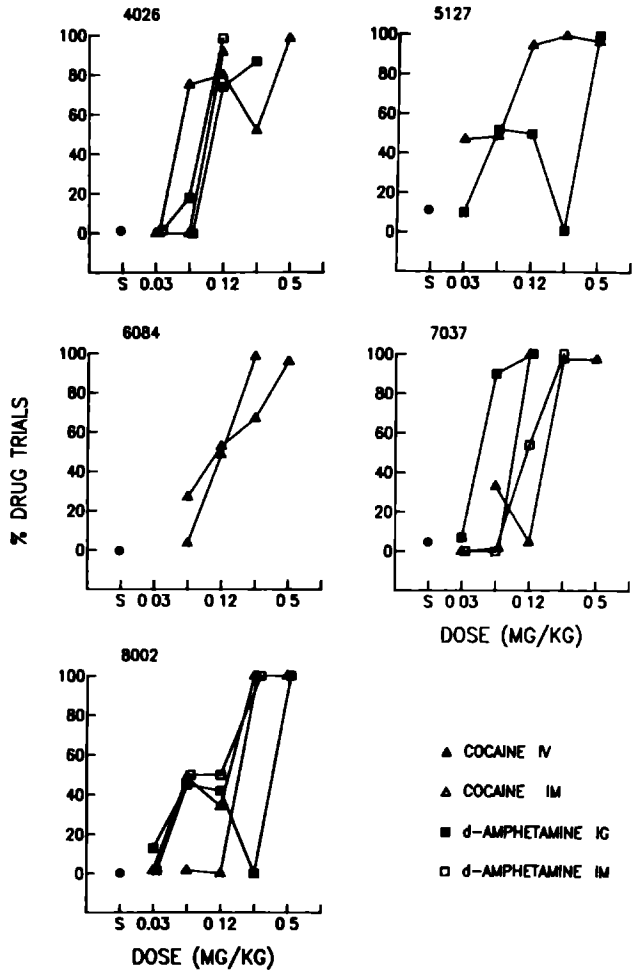

Fig 1 The percent of trials completed on the cocaine-appropriate lever as a function of dose and route of administration during test sessions The point above saline (S) is the mean of all saline test days obtained during the determination of all the dose response functions

discriminative stimulus (DS) effects Rhesus monkeys were initially trained to discriminate IM cocaine from saline and subsequently cocaine was tested after IM, IV, and IG administration In addition, substitution patterns for IM and IG *d*-amphetamine were also obtained

METHOD

Subjects

Five rhesus monkeys were used in this study The subjects weighed between 8 and 10 kg and were housed in stainless steel cages They were given ad lib food and water after each experimental session All subjects had previous experimental histories in self-administration and other studies of schedule-controlled performance using a variety of psychoactive drugs

TABLE 1

PERCENT TRIALS COMPLETED ON COCAINE-APPROPRIATE LEVER AFTER IG COCAINE GIVEN 60 MIN PRIOR TO THE SESSION

Monkey	4026		6084		7037	
Determination	1	2	1	2	1	2
Dose (mg/kg)						
0 5	0					
1 0	100*	0*	10*	80	21	0*
2 0	100	0*	0	10*	0	100*
4 0	13*		7*	0	97	0*
8 0	47*		33	100*	97	100*
16 0			100*	30	100*	

*Cocaine (0 25 mg/kg, IM) administered on immediately preceeding training session Otherwise saline had been administered

Apparatus

During experimental sessions, each monkey was seated in a primate restraining chair (Plas-Labs, Lansing, MI) which was housed within a wooden cubicle (85×64×175 cm) A Plexiglas plate was attached to the chair perpendicular to the body of the animal to prevent responding occurring on both levers simultaneously The cubicle was equipped with two primate levers (PRL-001, BRS/LVE) mounted on metal boxes (15×13×10 cm) and located below four white Dialco stimulus lights The levers were 24 cm apart and 99 cm above the floor of the cubicle Another metal box (13×23×15 cm) was mounted on the ceiling of the cubicle This box had a clear Plexiglas cover and contained a white bulb that served as houselight A fan mounted on the ceiling provided ventilation and masking noise

The monkeys' feet were placed into shoes mounted on the chair Brass plates were permanently fitted inside the shoes to allow the delivery of electric shocks Shocks were delivered by a shock generator (SG-903, BRS/LVE) located outside the cubicle Cables connected the cubicle to solid state programming and recording equipment located in an adjacent room

Procedure

A trial procedure was used to train the monkeys to avoid or escape the delivery of electric shocks Initially only the right lever was presented Trials were initiated with the illumination of the houselight and the lights above the lever A shock period began five seconds after the initiation of the trial During this period, shocks were delivered every 2 sec (250 msec in duration, 10 mA in intensity) until a response occurred (escape) Immediately after a response occurred, the houselight, lever lights, and shocks were terminated If a response occurred before the 5 sec period had elapsed, the houselight and lever lights were terminated and no shocks were delivered (avoidance) In both cases a 55 sec inter-trial interval (ITI) followed before a new trial was initiated During the ITI the cubicle remained dark The session lasted until 30 trials were completed or until 40 min had elapsed, whichever came first When the avoidance response occurred on more than 90% of the trials for 3 consecutive sessions, the left lever was made operational and the right lever was covered The same contingencies remained in effect

until 90% of the trials were avoidance for 3 consecutive sessions Thereafter, the operational lever was changed daily and, concurrently, appropriate drug injections were administered 10 min prior to the session The right lever was operative after the administration of cocaine (0 25 mg/kg, IM) for three of the monkeys (4026, 6084, 8002) and the left for the other two (5127, 7037) The other lever was operative after saline These conditions remained in effect until 5 consecutive sessions with more than 90% avoidance trials were obtained Initially, the front of the restraining chair was placed flush with the lever boxes However, the chair was slowly removed from the lever boxes so that a monkey had to extend its arm to depress the lever The distance between the chair and the lever boxes was increased to prevent simultaneous responding on both levers

During the next phase of training, the monkeys were presented with both levers for the first time The lever that terminated the trial was made conditional upon cocaine or saline administration, but all other conditions remained as previously described If a correct avoidance or escape response occurred, i e , a response on the lever associated with the drug condition, the trial was terminated If the monkey responded on the incorrect lever, a change-over delay (COD) period was started During this period, responding on the correct lever did not terminate the trial until 2 seconds had elapsed since the last incorrect response (COD 2 sec) Further incorrect responses reset the COD timer Correct responses during the COD period was signalled by a brief flicker of the houselight and lever lights A trial was counted as correct when no incorrect responses were emitted

An additional procedure was introduced to facilitate discrimination training The ITI was reduced to a few seconds at the start of the training session, but all other conditions remained the same After several responses on the correct lever, without incorrect responses, the ITI was increased during the session in small increments (approximately 5 to 10 sec at a time) provided the subject continued responding on the correct lever This procedure was continued until the monkey's performance remained above 90% correct over several sessions with the ITI reaching 55 sec for at least a portion of the session Subsequently, the monkey was reintroduced to the initial condition in which the ITI was 55 sec throughout the entire session

Initially, cocaine and saline injections were alternated on a daily basis When five consecutive sessions under the terminal contingencies occurred with more than 90% correct trials, the drug conditions were presented in a sequence that was random except that no condition could occur more than twice in a row All other conditions remained the same

When six consecutive sessions of more than 90% correct trials were obtained, the ability of other cocaine doses, administered by the IM, IV, or IG route, to control drug-appropriate responding was determined during test sessions Similar dose-effect functions were obtained with IM and IG *d*-amphetamine When these drugs were tested IG, the drug solutions were generally given 60 min prior to the session For the other routes, drug solutions were given 10 min prior to the session During test conditions, responding on either lever terminated the trial but all other conditions remained the same Each dose of a drug was generally given twice by each route All doses of a compound were presented in a mixed order and tested before a new route or drug was tested Test sessions occurred no more frequently than twice a week and at least 2 training sessions intervened Not all monkeys were tested with all routes and drugs

Data Analysis

The percent of total responses that occurred on the cocaine lever during test sessions was used as a measure of drug substitution The cumulative latency from the onset of the trial to its termination was used as a measure of nonspecific drug effects

Drugs

d-Amphetamine sulfate and cocaine hydrochloride were obtained from the National Institute on Drug Abuse Both drugs were dissolved in physiological saline and drug doses were calculated from the salt

RESULTS

Figure 1 shows that cocaine administered IM to five monkeys (0 03–0 5 mg/kg) or IV to four monkeys (0 03–0 25 mg/kg) controlled cocaine-appropriate responding in a dose-dependent manner Cocaine did not increase the latency to the first response relative to saline by either route (data not shown) *d*-Amphetamine (Fig 1) delivered IM or IG to four monkeys (0 03–0 5 mg/kg) controlled cocaine-appropriate responding in a dose-dependent manner at doses that did not increase the latency to respond

When cocaine was administered IG 60 min pre-session, it controlled criterion levels (90%) of cocaine-appropriate responding in all 3 monkeys tested at some dose (Table 1) In monkey 7037, tested with IG cocaine with a 10 min pretreatment, the administration of the same range of doses led to saline-appropriate responding However, as shown in Table 1, responding at the 60 min pretreatment time was not dose-dependent and there was considerable variability across redeterminations The variability did not appear related to the drug administered the day prior to testing or order (first vs second determination) Two of the three monkeys died after the administration of 8 mg/kg (4026) or 16 mg/kg (6084) Monkey 6084 died of convulsions at least 8 hours after the infusion and 4026 died of kidney and liver complications 2 days after the infusion

Although it is difficult to estimate the potency of IG cocaine because of the variability, relative to cocaine given IV or IM or *d*-amphetamine given IM or IG, it was less potent All the other dose-response functions were similar regardless of drug or route of administration

DISCUSSION

Cocaine and *d*-amphetamine regardless of route of administration controlled drug-appropriate responding in monkeys trained to discriminate IM cocaine from saline Except when cocaine was delivered IG cocaine and *d*-amphetamine were similar in potency Although the variability of the IG cocaine results was too great to accurately estimate potency relative to the other functions, IG cocaine was at least 2 fold less potent in each of the monkeys tested In rhesus monkeys, similar effects of cocaine and *d*-amphetamine have been reported in studies that compared the effects of these drugs given by different routes of administration on behavior maintained under a variable-interval schedule of food delivery Downs *et al* [2] showed that cocaine, given orally, was 16 times less potent than IM or IV cocaine when administered 30 min before the session *d*-Amphetamine given by the IM, IV and IG routes also produced similar dose-dependent decreases in response rates compared to IM and IV cocaine Likewise, in the present experiment, IV cocaine, IM co-

caine, IM *d*-amphetamine and IG *d*-amphetamine were equipotent in their ability to control cocaine-appropriate responding whereas IG cocaine was less potent

Until recently, it was generally accepted that cocaine when taken orally was inactive [4] However van Dyke *et al* [5] showed that orally administered cocaine produced detectable cocaine plasma levels and subjective effects 30 min after its delivery Peak plasma levels and subjective effects occurred, however, between 50 and 90 min after administration The results of the present study also demonstrate that cocaine delivered directly into the stomach is active In each of the monkeys tested, IG cocaine controlled 100% drug-appropriate responding at some dose However, the results were extremely variable in that the effects were not related clearly to dose and there were failures to replicate when doses were tested a second time These inconsistent results may have been due to erratic absorption Cocaine is not well absorbed in the highly acidic stomach and must pass to the small intestine where absorption of basic compounds is more efficient The failure of cocaine to produce drug-appropriate responding after a 10 min pretreatment in the present study was presumably because not enough drug had passed from the stomach to the small intestine during testing Likewise, the results with the longer pretreatment time may indicate that other factors, such as cocaine's vasoconstrictive properties, result in variable rates of absorption Clearly further research is needed to describe the role of these other pharmacokinetic factors in the behavioral effects of IG cocaine Nevertheless, regardless of variability the present results further demonstrate that oral cocaine is not inactive Furthermore, the delayed death seen in two monkeys indicates that oral cocaine has significant toxicity of unknown mechanism

REFERENCES

1 Ando, K and T Yanagita The discriminative stimulus properties of intravenously administered cocaine in rhesus monkeys In *Stimulus Properties of Drugs Ten Years of Progress* edited by F C Colpaert and J A Rosecrans Amsterdam Elsevier Biomedical Press, 1978, pp 125–136

2 Downs, D A , L W Miller, J N Wiley and D E Johnston Oral vs parenteral drug effects on schedule-controlled behavior in rhesus monkeys *Life Sci* **26**, 1163–1168, 1980

3 Garza, R de la and C E Johanson The discriminative stimulus properties of cocaine in the rhesus monkey *Pharmacol Biochem Behav* **19**, 145–148, 1983

4 Ritchie, J M , P J Cohen and R D Dripps Cocaine, procaine and other synthetic local anesthetics In *The Pharmacological Basis of Therapeutics* edited by L S Goodman and A Gilman New York MacMillan, 1970, pp 155–168

5 Van Dyke, C , P Jatlow, J Ungerer P G Barash and R Byck Oral cocaine Plasma concentration and central effects *Science* **200** 211–213, 1978

6 Woolverton, W L and R C Trost Cocaine as a discriminative stimulus for responding maintained by food in squirrel monkeys *Pharmacol Biochem Behav* **8** 627–630, 1978