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Discriminative Stimulus Properties of Cocaine, Norcocaine, and N-Allylnorcocaine[1]

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BEDFORD, J. A., G. L. NAIL, R. F. BORNE AND M. C. WILSON. *Discriminative stimulus properties of cocaine, norcocaine, and n-allylnorcocaine.* PHARMAC. BIOCHEM. BEHAV. 14(1) 81–83, 1981.—A discriminative stimulus paradigm was employed to train eight male and female Wistar rats to discriminate 5.0 mg/kg cocaine HCl from 2.0 ml/kg saline. Subjects responded in a two bar operant chamber on an FR 30 schedule for food reinforcement. All sessions followed a 10 minute pretreatment with either saline, the training dose of cocaine, four probe doses of cocaine HCl (1.0, 2.5, 7.5, 10 mg/kg), four probe doses of norcocaine (1.0, 2.5, 5.0, 7.5 mg/kg) or four probe doses of N-allylnorcocaine (5.0, 7.5, 10, 20 mg/kg). All probe doses were tested using an extinction procedure. The three highest doses of cocaine generalized to cocaine while the 1.0 mg/kg dose of cocaine generalized to saline. The two highest doses of norcocaine generalized to cocaine while the 2.5 mg/kg dose of norcocaine resulted in 57% responding on the cocaine lever with the 1.0 mg/kg dose generalizing to saline. Only the highest dose of N-allylnorcocaine was found to generalize to cocaine with the intermediate doses resulting in an intermediate level of responding occurring on the cocaine lever. The 5.0 mg/kg dose of N-allylnorcocaine generalized to saline.

Cocaine Norcocaine N-Allylnorcocaine Stimulus properties Rats

PREVIOUS reports have demonstrated that the majority of a dose of cocaine administered either to man or to several laboratory species is hydrolyzed by blood and liver enzymes to form the two major metabolites, benzoylecgonine and ecgonine [4, 8, 9, 11, 13]. Further studies have also shown that some of the cocaine is demethylated to form norcocaine [5, 8, 10]. In addition it has also been demonstrated that norcocaine is an active metabolite and possesses stimulus properties similar to those of cocaine [7].

Previous work in this laboratory led to the synthesis and subsequent pharmacologic testing of the N-allyl derivative of norcocaine [6]. Our initial interest in this compound was to determine if it might possibly show an antagonistic relationship to cocaine as nalorphine does to morphine. Unpublished data from this laboratory as well as another published report [12] demonstrate that N-allylnorcocaine does not antagonize the effects of cocaine on locomotor activity. Furthermore, the physiological profile of this compound differed somewhat from that of cocaine in monkeys [6].

The purpose of the present study was to determine whether norcocaine and N-allylnorcocaine shared the stimulus properties of cocaine.

METHOD

Subjects

The subjects were eight male and female Wistar rats (Harland Industries, Cumberland, IN) weighing between 200–250 g at the start of the experiment. Subjects were reduced to and maintained at 85% of their free feeding weight for the duration of the experiment. Water was freely available except during experimental sessions. When not in the experimental chambers, subjects were maintained in individual galvanized steel cages. Ambient temperature was maintained at 21 ± 1°C and the light/dark cycle was 12 hr on, 12 hr off.

Apparatus

Standard operant conditioning chambers (BRS-LVE, Beltsville, MD) measuring 39 cm long and 39 cm high by 39 cm wide were contained in sound attenuating enclosures (BRS-LVE). Two rodent response levers (BRS-LVE) were located 10 cm from the wire mesh floor and 7.0 cm from the front and rear walls respectively. A food cup was located equidistant between the two levers and 1 cm from the floor. Three jeweled panel lights were located 5 cm above each

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lever. Ambient illumination was provided by two 28 V DC panel lights located behind a transparent panel near the top of the chamber. Forced air ventillation provided a continuous air exchange, and also served as a source of masking noise.

Drugs and Solutions

Drug solutions for this experiment were prepared on the morning of use. All dosages were calculated on the basis of the hydrochloride salt. Cocaine hydrochloride flakes U.S.P. were obtained from Mallinckrodt Chemical Corp. (St. Louis, MO). Norcocaine HCl and N-allylnorcocaine HCl were prepared and analyzed by two previously reported methods [3,6].

Procedure

Experimental sessions were conducted daily, 5 days per week and were 8 min long. Following initial bar press training, 5 mg/kg cocaine HCl in 2 ml/kg sterile 0.9% saline or 2 ml/kg saline were administered IP 10 min prior to each session. Reinforcement (45 mg pellets, P. J. Noyes, Lancaster, NH) was contingent upon pressing the lever appropriate to the type of pretreatment on a given day. The lever designated the cocaine lever and the lever designated the saline lever were determined randomly for each subject. The pretreatment sequence followed throughout the study, except on probe sessions was as follows: Cocaine-saline-saline-cocaine, saline-cocaine-cocaine-saline, etc. During the initial discrimination training sessions the reinforcement schedule in effect was FR1 (i.e. each bar press on the appropriate lever was reinforced), however the schedule requirement was gradually increased to a final value of FR30 (i.e. every 30th response on the appropriate lever was reinforced) and maintained at this value throughout the study. Once discrimination behavior had stabilized (stability criterion—85% responding on correct lever) probe tests were begun. Probe tests were conducted on Friday of each week. A probe session consisted of pretreating each subject IP (10 min prior to being placed in the chamber) with one of four doses of either cocaine, norcocaine, or N-allylnorcocaine. The four probe doses of each compound were as follows: cocaine—1.0, 2.5, 7.5, 10.0 mg/kg; norcocaine—1.0, 2.5, 5.0, 7.5 mg/kg and N-allylnorcocaine—5.0, 7.5, 10.0, 20.0 mg/kg. Each dose of each compound was tested once in separately randomized sequences. The subjects were allowed to respond until 90 responses had occurred on either of the bars, after which the subject was immediately removed from the chamber. No reinforcement occurred during probe sessions.

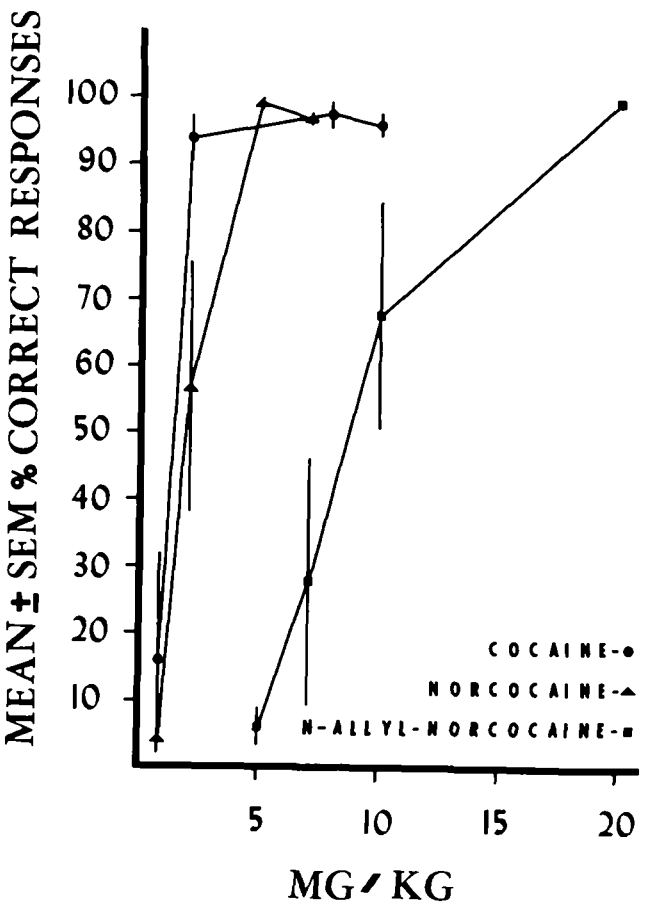

FIG. 1. Generalization tests conducted with cocaine, norcocaine and N-allylnorcocaine. Data points represent the mean percent response on the cocaine lever during probe tests. The verticle lines represent the standard error of measurement.

RESULTS

Figure 1 presents the dose response curve for cocaine, norcocaine and N-allylnorcocaine. The three highest doses of cocaine (2.5, 7.5, 10.0 mg/kg) generalized to cocaine with better than 90% of the responses occurring on the cocaine lever. The 1.0 mg/kg dose of cocaine generalized to saline with approximately 85% of the responses occurring on the saline lever. Norcocaine was shown to generalize to cocaine at the 5.0 and 7.5 mg/kg doses with greater than 95% of the responses occurring on the cocaine lever. The 2.5 mg/kg dose of norcocaine produced an intermediate number of responses on both levers whereas the 1.0 mg/kg dose generalized to saline with greater than 95% of the responses occurring on the saline lever. N-allylnorcocaine was found to generalize to cocaine only at the highest dose (20 mg/kg) tested with 99% of the responses occurring on the cocaine lever. The 7.5 and 10 mg/kg doses of this compound resulted in 28% and 68% respectively responses occurring on the cocaine lever, whereas the 5.0 mg/kg dose generalized to saline with 94% of the responses occurring on the saline lever.

DISCUSSION

The results obtained with norcocaine clearly support the other published report on the discriminative stimulus properties of norcocaine [7]. Although our generalization gradient for norcocaine and also cocaine was considerably steeper than this report, this difference may be accounted for by the difference in training dose (5.0 mg/kg in the present study vs 10 mg/kg in the prior study). This similarity in stimulus properties between cocaine and norcocaine is not surprising since norcocaine has been shown to be similar to cocaine in a number of situations. Both drugs produced a decrease in limited access food consumption in rats [1,2]. Likewise both drugs are intravenously self-administered by rhesus mon-

keys. In addition, cocaine and norcocaine produced similar decreases in response rate in rats maintained on a fixed-ratio food reinforcement schedule [2]. In contrast to the preceding similarities in effect, several instances of qualitative differences in activity have also been reported. Cocaine has been shown to produce a dose-related increase in response rate in rats maintained on a fixed-interval schedule of food reinforcement. However, norcocaine produced a dose-related decrease in rate on the same schedule [2]. In addition, cocaine produced a dose-related increase in locomotor activity in rats while norcocaine in the same dosage range did not alter activity [2]. Further increases in the dose of norcocaine in this study resulted in convulsion and death, indicating that the lack of effect of norcocaine on locomotor activity was not a result of dosage range. Finally the quantitative difference apparent between the 2.5 mg/kg doses of cocaine and norcocaine in the present paper supports previously published reports. Norcocaine produced a significantly greater reduction in food consumption than equal doses of cocaine, and in addition it appeared to be a somewhat more potent intravenous reinforcer in rhesus monkeys [2].

The results obtained with N-allylnorcocaine also support published reports concerning this compound [1,12]. The present results indicated that N-allylnorcocaine shares similar stimulus properties with cocaine. However, much higher doses were required to produce generalization. This apparent potency difference agrees with other published reports comparing the effects of N-allylnorcocaine to cocaine [1,12]. A recent report [1] demonstrated that although N-allylnorcocaine suppressed food consumption in rats, equal doses of cocaine produced a significantly greater reduction in food consumption, again indicating a potency difference between the drugs. Furthermore, like norcocaine, the pharmacological profile of N-allylnorcocaine appeared to be similar to cocaine, albeit somewhat less potent [6]. However, N-allylnorcocaine did not alter locomotor activity (unpublished observation). Therefore, with respect to actometric activity, N-allylnorcocaine more closely approximates norcocaine than it does cocaine.

The foregoing data clearly demonstrates that norcocaine and N-allylnorcocaine share similar stimulus properties with cocaine. However, potency differences were also quite apparent. The potency differences reported here are in general agreement with other published reports [1,12]. Possible explanations for these potency differences have been reported [12]. These authors offered a number of potential explanations for these differences (e.g. different lipid solubilities and/or rates of metabolism). In addition to these, other possible explanations could involve different dissociation constants or volumes of distribution. Research is currently underway in our laboratories in an attempt to resolve this question.

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