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BRIEF COMMUNICATION

Mazindol Self-Administration in the Rhesus Monkey[1]

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WILSON, M. C. AND C. R. SCHUSTER. *Mazindol self-administration in the rhesus monkey.* PHARMAC. BIOCHEM. BEHAV. 4(2) 207–210, 1976. – The ability of the intravenous administration of mazindol (SaH 42–548) to act as a reinforcer in monkeys previously conditioned to self-administer cocaine was ascertained. Unit dosages i.e. dosage per injection, of 50 and 100 μg/kg resulted in self-administration rates significantly greater than that which occurred with saline. An inverse relationship existed between unit dosage and frequency of self-administration over the unit dosage range 50–200 μg/kg. The total mazindol dosage self-administration per session was however independent of unit dosage. Approximately 2–3 mg/kg was self-administered by each animal during a 4 hr session at each of the 3 unit dosages. This tends to indicate that the 200 μg/kg unit dosage was also reinforcing even though the self-administration rate was similar to that of saline. This study indicates that mazindol can serve as a reinforcer and that the relationship between total session intake, unit dosage, and self-administration frequency of mazindol are similar to these seen with other reinforcing psychomotor stimulant drugs.

Mazindol Drug self-administration Cocaine

IT has previously been demonstrated by several investigators that rhesus monkeys can be conditioned to emit a response which results in the intravenous administration of psychomotor stimulant drugs including cocaine, d-amphetamine, and caffeine [2, 3, 5, 6]. When access to cocaine is limited to four hours daily, the frequency of self-administration behavior becomes very stable within two weeks. If the unit dosage i.e. dosage per injection, is manipulated within a range of reinforcing values, i.e. dosages that maintain responding; the frequency of the behavior is altered in such a manner that total session drug intake remains stable for each animal. Therefore with cocaine, an inverse relationship exists between unit dosage and the frequency of self-administration behavior.

If the cocaine is replaced with another psychomotor stimulant drug for several sessions, the frequency and stability of self-administration behavior emitted during this period is a function of the reinforcing action exhibited by the substitute compound. Using such a substitution procedure the reinforcing actions of pipradrol, methylphenidate, phenmetrazine [5], and d-amphetamine, l-amphetamine and methamphetamine [1] have been demonstrated. If the appropriate dosage of a reinforcing drug is substituted for cocaine, self-administration behavior will be maintained at a rate significantly higher than with saline. In addition, for drugs of the psychomotor stimulant class, the frequency of self-administration behavior is inversely related to unit dosage.

If a nonreinforcing substance such as saline is substituted for the cocaine, the frequency of self-administration behavior will fall to the operant level usually within 3–5 sessions. However, on the initial day of saline substitution, especially during the first part of the session, self-administration behavior may exceed that seen with the previous unit dosage of cocaine. This appearance of extinction responding further demonstrates the reinforcing action of cocaine. This substitution procedure therefore seems to be a useful first stage in predicting whether a drug can act as a reinforcer.

Recently a new anorexic drug, mazindol, (SANOREX® SaH 42–548) has been introduced in the United States by Sandoz Pharmaceuticals. This compound is not a phenethylamine derivative unlike most anorexic psychomotor stimulants. However, in addition to its anorexic effect it does produce increased locomotor activity hyperexcitability and tremors in rats, and stimulation of continuous avoidance behavior in rats and squirrel monkeys. (Sandoz Pharmaceuticals: personal communication). Therefore, mazindol possesses a central pharmacological spectrum which is somewhat similar to that exhibited by those

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psychomotor stimulants whose reinforcing effect has already been demonstrated in rhesus monkeys. Therefore, it would appear to be highly desirable to ascertain the ability of this compound to act as a reinforcer.

METHOD

Animals and Apparatus

The animals for this study were 4 adult male rhesus monkeys weighing 3.5–4.7 kg. The animals were continuously individually housed in open-faced experimental cubicles constructed of stainless steel and nontransparent white plastic [5]. Water was available ad lib and Purina Monkey chows were provided twice daily. The animals were restrained in these cubicles by a stainless steel harness and arm [2]. Indwelling jugular catheters of siliconized rubber had been previously implanted in the right internal jugular vein. Each depression of a response lever, located on the back wall of the cubicle, with at least 100 g of force, resulted in the intravenous administration of 200 μg/kg of cocaine hydrochloride dissolved in sterile physiological saline. The injection volume in all cases was 0.2 ml/kg of body weight. Cocaine was available daily from 10:00 a.m. until 2:00 p.m. and access during this period was limited only by the duration of an injection cycle which lasted approximately 50 sec. The onset of the period of drug availability was indicated by the illumination of a stimulus light located directly above the response lever. This light remained illuminated for the entire 4 hr period. A programmed injection occurred every 4 hr between sessions in an attempt to retard catheter occlusion via clot formation. Under these conditions the daily intake of cocaine was very stable within animals with only a 10% variability in total drug intake occurring from day to day. However, there was some difference in total session intake across animals.

Procedure

Three different unit dosages of mazindol (SaH 42–548) i.e., 50, 100, 200 μg/kg were substituted for cocaine in each of the 4 animals. The sequence of dosage testing was randomized for each of the animals. Each dosage was substituted for cocaine for 5 consecutive sessions. Solutions of mazindol were prepared on the first and third days of each substitution block of 5 sessions. In addition, saline was substituted for cocaine in an identical fashion in each animal. Between the testing of each dosage level of SaH 42–548 and saline, the animals were returned to 200 μg/kg of cocaine for 3 sessions to allow the frequency of self-administration behavior to return to baseline levels. In addition, this insured that the standard drug, cocaine, still exhibited reinforcing efficacy.

The frequency of self-administration behavior across animals occurring during the last 3 sessions of substitution with saline were compared via the Student's *t* test to that occurring during the last 3 sessions of SaH 42–548 substitution for each dosage. Only the last 3 days of data were utilized in data analysis in order to avoid analytical confusion produced by extinction responding. Even if SaH 42–548 were not reinforcing, responding during the initial 2 days of substitution may have occurred due to (1) extinction of primary cocaine reinforcement and/or (2) extinction of conditioned reinforcers i.e., auditory stimuli of pump activation, previously associated with cocaine reinforced responding. Previous experience in this laboratory has demonstrated that responding resulting from these factors is insignificant after 2 substitution sessions have been concluded.

RESULTS

The results of this study are illustrated in Fig. 1. Unit dosages of 50 and 100 μg/kg of SaH 42–548 were self-administered at a statistically significant greater frequency than saline; however, the 200 μg/kg dosage was not. None of the unit dosages of SaH 42–548 were self-administered at a frequency comparable to that which occurred with the baseline unit dosage of cocaine. The mean number of self-administrations per session for cocaine, saline, 50 μg/kg of SaH 42–548, 100 μg/kg of SaH 42–548 and 200 μg/kg of SaH 42–548 respectively, were 85, 9, 39, 27 and 13. In general, the pattern or rate of SaH 42–548 self-administration during a session was fairly constant for a given animal. During the initial 15 min of the session there characteristically was a burst of responding. However, during the remainder of the session the pausing between succeeding injections was very stable and was directly proportional to the unit dosage of SaH 42–548. This is illustrated in the left hand graph in Fig. 1 by the inverse relationship which existed between unit dosage and self-administration frequency. The right hand graph in Fig. 1 demonstrates that total session intake was independent of unit dosage for those unit dosages of SaH 42–548 which were tested. Even though a 4-fold difference existed in unit dosages, adjustments were made in the frequency of self-administration so that the result was a nonsignificant effect on total drug intake during the session. Even though the frequency of the lever-press behavior emitted for the 200 μg/kg dosage of SaH 42–548 was not statistically different from that emitted for saline, the amount of SaH 42–548 self-administered at this dosage was equivalent to that self-administered at the 2 lower unit dosages.

No significant trends i.e., order effects; were observed between the sequence of unit dosages tested and the total amount of SaH 42–548 administered per session.

During the sessions in which SaH 42–548 was self-administered there was gross evidence of enhanced locomotor activity as compared to saline control sessions. Furthermore, mydriasis, salivation and muscle tremors were exhibited during periods of mazindol intake.

DISCUSSION

The results of this study demonstrate that the intravenous administration of mazindol will maintain lever-press behavior in animals previously conditioned to self-administer cocaine. The inverse relationship between frequency of responding and unit dosage is typical of other drugs with similar pharmacological actions. Previous investigations have demonstrated this relationship with cocaine [3, 5, 6], phenmetrazine, pipradrol, and methylphenidate [5], and with d-amphetamine, l-amphetamine and methamphetamine [1]. Total session intake of these agents as well as of mazindol is relatively independent of unit dosage over the range of unit dosages found to be reinforcing. The mechanism responsible for this consistency of total session intake is presently unknown. It has been hypothesized that aversive or nonspecific behavioral disruptive actions of the psychomotor stimulants may be responsible for limiting their own self-administration [1,5].

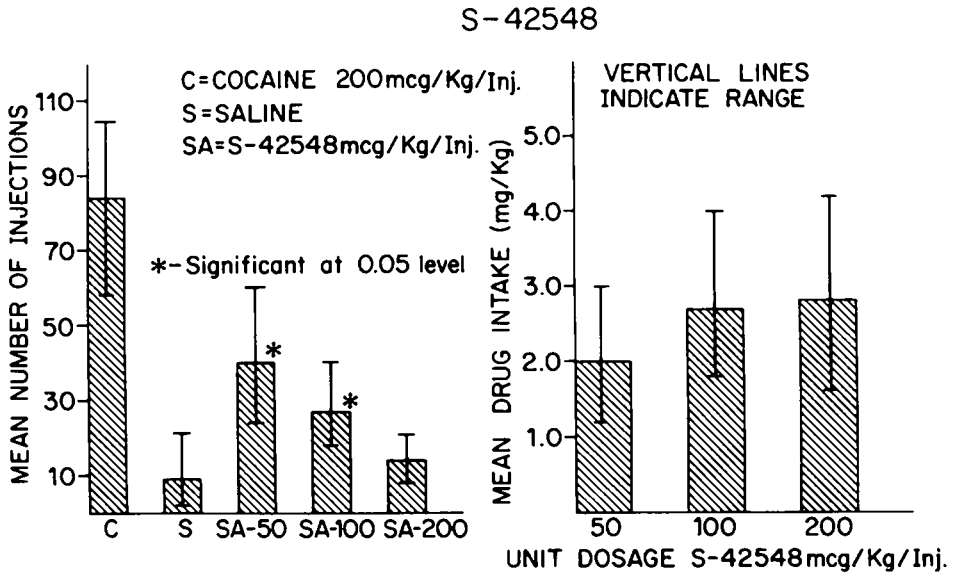

FIG. 1. (Left side). Mean number of injections per session as a function of the unit dosage of SaH 42–548 as compared to saline and the baseline unit dosage of cocaine. The height of the cross-hatched bars for saline and SaH 42–548 represent the mean number of injections per session occurring during the last three days of substitution for all 4 animals. The height of the bar representing cocaine indicates the mean number of cocaine self-administrations occurring during the last 3 days of cocaine self-administration prior to the first substitution block of 5 sessions and during the final session of cocaine self-administration occurring between blocks of substitution sessions. The superimposed vertical bars represent the range of values for these sessions. (Right side). Mean session intake of SaH 42–548 as function of the unit dosage of SaH 42–548. Means were obtained by using data from the last three substitution sessions at each dosage for each animal. The superimposed vertical lines represent the range of SaH 42–548 intake for these sessions in all animals.

Apparently a similar mechanism may be operative in controlling the frequency of mazindol self-administration. Therefore, when similar procedures are utilized, intravenous mazindol self-administration behavior resembles that of other psychomotor stimulants.

The concept of using the rate of self-administration behavior as a measure of reinforcement efficacy is challenged by the results of this study. The apparent optimum reinforcing dosage of mazindol over a 4 hr session is 2–3 mg/kg. If one based the decision as to whether a unit dosage of 200 μg/kg was reinforcing, and used the rate of self-administration behavior as his criterion, then this dosage would not be reinforcing since it was not self-administered at a frequency greater than saline. However, if one calculates total session intake of mazindol when the unit dosage was 200 μg/kg, the amount of drug self-administered during the session was very similar to that occurring during sessions in which the unit dosage was 50 or 100 μg/kg. Furthermore, there is no evidence that the 50 μg/kg unit dosage was more reinforcing than either the 100 or 200 μg/kg. Such comparisons as to relative reinforcing efficacy await the utilization of more complex behavioral procedures. Johanson and Schuster [4] have reported on a choice procedure which was designed to assess the relative reinforcing efficacy of different psychomotor stimulants. When given the opportunity to self-administer either a low or higher unit dosage of cocaine (0.05–1.5 mg/kg) animals preferred the higher dose except when both dosages were greater than 0.5 mg/kg. Similarly higher doses of methylphenidate were preferred to lower doses of methylphenidate. This finding tends to confirm the hypothesis that the inverse relationship exists between response rate and unit dosage when animals have limited daily access to psychomotor stimulants [1, 3, 5, 6] does not indicate that lower dosages are more reinforcing than higher dosage. When equal doses of cocaine and methylphenidate were compared no preference was shown. On other comparisons between the drugs, the higher dose was generally preferred regardless of the drug. The magnitude of reinforcement produced by intravenously self-administered stimulants must be assessed not only on response rate maintained on reinforcement schedules but also with reference to concurrently available drugs.

Because the frequency of cocaine self-administration was greater than that of mazindol, should not lead one to readily assume that cocaine is a more efficacious reinforcer than mazindol. It is possible that comparble rates of responding for mazindol would have been obtained if lower unit dosages had been studied. Further this difference in rate may be a reflection of the difference in the relative duration of action of the two drugs. Because of this one should not necessarily expect unit dosages of different psychomotor stimulants which produce equal response rates on a CRF schedule e.g. 50 μg/kg mazindol, 800 μg/kg cocaine, 200 μg/kg pipradrol, 200 μg/kg of methylphenidate and 300 μg/kg of phenmetrazine to be equally reinforcing under more complex schedules of reinforcement [4]. Factors such as duration of action per unit dosage as well as other determinants of the frequency of this behavior must first be assessed before reinforcement efficacy is

adequately compared. Certainly no comparison of the relative reinforcing efficacy of mazindol should be made with that of other psychomotor stimulants strictly on the basis of this initial study. This study indicates that (1) intravenous presentation of mazindol can serve as a reinforcer and that (2) the relationships between total session intake, unit dosage, and self-administration frequency of mazindol are similar to those seen with other reinforcing psychomotor stimulants.

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