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Behavioral Tolerance and Cross-Tolerance to *dl*-Cathinone and *d*-Amphetamine in Rats[1]

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ABSTRACT

The effects of *dl*-cathinone (0.25–48 mg/kg, i.p.) and *d*-amphetamine (0.25–8.0 mg/kg, i.p.) on milk intake in rats were determined before, during and after a period of repeated daily administration of *dl*-cathinone. Experimental sessions consisted of 15-min access to a sweetened milk solution each day, 7 days a week. After the determination of the acute effects of *dl*-cathinone and *d*-amphetamine on milk intake, rats were injected daily with either 4.0 mg/kg of *dl*-cathinone 15 min before each session and saline 15 min after each session; or saline 15 min before each session and 4.0 mg/kg of *dl*-cathinone 15 min after each session. Milk intake returned toward base-line levels for animals receiving daily *dl*-cathinone before the session over a period of 16 sessions, and remained slightly decreased compared to animals that received postsession injections. Dose-response functions for *dl*-cathinone and *d*-amphetamine were then redetermined by substituting a test dose for the usual presession injection once every 4 to 5 days. In animals that were receiving presession *dl*-cathinone, both drugs had less effect, indicating the development of tolerance to *dl*-cathinone and cross-tolerance to *d*-amphetamine. The development of tolerance to the suppression of milk drinking was contingent upon the relationship of the time of the daily injection to milk availability. Animals that were receiving *dl*-cathinone after the session did not develop tolerance but were more sensitive to the effects of both drugs on milk intake. Dose-response functions for both drugs determined after 10 drug free days were similar to the initial dose-response functions, indicating the transient nature of the tolerance and supersensitivity.

Cathinone [(−)-α-aminopropiophenone] is an alkaloid that has been isolated from the fresh leaves of *Catha edulis*, a perennial shrub. These leaves are chewed by the natives of certain eastern African countries presumably for the amphetamine-like central nervous system effects produced by cathinone (Halbach, 1972, 1980; Luqman and Danowski, 1976). Both the chemical structure and many of the behavioral effects of cathinone are similar to those of amphetamine. For instance, both substances function as positive reinforcers and disrupt food-maintained behavior in rhesus monkeys (Johanson and Schuster, 1979, 1981) and suppress food intake in rats (Knoll, 1980; Zelger and Carlini, 1980). Rats trained to discriminate amphetamine from saline respond on the amphetamine-appropriate lever when given *l*-cathinone (Rosecrans *et al.*, 1980). In addition, *d*-amphetamine and cathinone are equally effective in increasing locomotor activity (Kalix, 1980a; Knoll, 1980; Yanagita, 1980; Zelger *et al.*, 1980) and producing hyperthermia in rats (Halbach, 1972) and rabbits (Kalix, 1980b). Finally, both cathinone and amphetamine can induce gustatory avoidance responses in rats (Foltin and Schuster, 1981).

Tolerance and cross-tolerance to the effects of cathinone and amphetamine on food intake recently have been reported (Zelger and Carlini, 1980) which indicates the possibility of a common mechanism of action. In that regard, Kalix (1980c, 1981) have found that both drugs enchance release of dopamine and G. C. Wagner, K. L. Preston, G. A. Ricaurte, L. S. Seiden and C. R. Schuster (personal communication) have found that chronic high dose treatment with either compound results in a significant depletion of dopamine in the caudate, telencephalon and midbrain of rats.

In addition to biochemical mechanisms, behavioral factors can also influence the rate of development and the extent of tolerance (Schuster *et al.*, 1966). Many studies indicate that tolerance to the suppressant effects of stimulants on food intake only develops in animals given amphetamine (*e.g.*, Campbell and Seiden, 1973; Carlton and Wolgin, 1971) or cocaine (Woolverton *et al.*, 1978a) before the daily feeding session and not in animals given similar amounts of the drug after each session. That is, experience with the drug while performing the behavior appears to be necessary for the development of tolerance.

To characterize the behavioral effects of cathinone further in comparison to those of *d*-amphetamine as well as to assess tolerance development, injections of cathinone were given to

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one group of animals before the experimental session and to another group after the session. In addition, the extent and duration of tolerance to cathinone and cross-tolerance to *d*-amphetamine were determined by completing dose-response functions before, during and after this period of daily injections of cathinone.

Methods

Animals and apparatus. Twenty male Sprague-Dawley rats (Holtzman, Madison, WI) weighing between 350 and 450 g at the start of the experiment were individually housed in ceiling-suspended stainless steel cages with water available *ad libitum* except during the experimental sessions. Sweetened condensed milk (Borden's Co., Columbus, OH; 1:2, milk/tap water) was presented in Wahmann (Baltimore, MD) 100-ml calibrated bottles attached centrally to the front of the cages. Supplemental feedings of 4 to 6 g of rat chow (4% Mouse and Rat Diet, Teklad Incorporated, Winfield IA) were given following each experimental session. A 6:00 A.M. to 6:00 P.M. light-dark cycle was maintained in the colony room with a constant temperature of 22°C.

Procedure. Experimental sessions consisting of a single 15-min presentation of milk occurred at the same time each day (10:00–10:15 A.M.), 7 days a week. Animals were weighed daily 15 min before the session. After stabilization of daily intake (less than 10% variation in mean intake for three consecutive days), physiological saline injections were given 15 min before the session for 4 consecutive days.

Dose-response functions were determined before, during and after a period of repeated administration of *dl*-cathinone. For the first dose-response determination, animals were randomly assigned to one of two groups of 10 rats each, with one group receiving *d*-amphetamine (0.5–4.0 mg/kg) and the other group receiving *dl*-cathinone (0.25–8.0 mg/kg). Test doses were administered in ascending order with all animals receiving all doses and at least 3 days of saline injections separating drug doses. Each of the two groups of rats was divided into two subgroups of five rats each that differed in daily drug treatment. All rats received physiological saline and drug injections, one before the session and one after the session. The difference between the groups was the time of the drug injection. The presession group received a dose of *dl*-cathinone (4.0 mg/kg) that decreased mean milk intake by at least 50% 15 min before the session, and the postsession group received the same dose of *dl*-cathinone 15 min after the session. After stabilization of milk intake during the period of repeated administration, dose-response functions for *dl*-cathinone and *d*-amphetamine were again determined. A test dose of drug was substituted for the usual presession injection once every 4 to 5 days with all rats receiving physiological saline postsession. The amphetamine groups were tested with *d*-amphetamine and the cathinone groups were tested with *dl*-cathinone with all animals receiving all doses given in an ascending order. After the last test dose, the repeated administrations were terminated and all rats received 10 consecutive days of physiological saline injections 15 min before each session. The dose-response functions for *d*-amphetamine and *dl*-cathinone were then redetermined using the same procedure as in the before repeated administration dose-response determination.

This resulted in four subgroups. In one group dose-response determinations for *d*-amphetamine were determined before, during and after the repeated administration of *dl*-cathinone given presession. In another group dose-response functions for *d*-amphetamine were determined before, during and after the repeated administration of *dl*-cathinone given postsession. For the third group dose-response functions were determined for *dl*-cathinone before, during and after the repeated administration of *dl*-cathinone given presession. The dose response functions for *dl*-cathinone were determined before, during and after repeated administration of *dl*-cathinone given postsession in the fourth group.

Drugs. *d*-Amphetamine sulfate, provided by the National Institute on Drug Abuse, and *dl*-cathinone hydrochloride, provided by the United Nations Narcotics Laboratory, were dissolved in physiological saline. All doses were given i.p. in a volume of 1 ml/kg and are expressed as weight of the salt.

Data analysis. Drug effects are expressed as percentage of base-line milk intake calculated separately for the group receiving *dl*-cathinone presession and *dl*-cathinone postsession by determining the intake for the 2 days before the injection of each test dose of drug. Mean base-line intake is a combination of all these pairs of days for each dose-response determination. ED_{50} values with 95% confidence limits were determined for the linear portion of each dose-response curve. Two dose-response functions were considered significantly different if the ED_{50} for each function was not within the 95% confidence interval of the other.

Results

Dose-response determinations. Mean base-line milk intake and S.E.M. for the dose-response function determined before the period of repeated administration was 35.1 ± 1.5 ml for the presession group and 33.1 ± 1.5 ml for the postsession group. After milk intake had stabilized for both groups during the period of repeated drug administration, base-line milk intake had decreased to 27.9 ± 2.5 and 30.9 ± 2.1 ml for the pre- and postsession, respectively. Finally, base-line milk intake returned to initial levels for both groups after the period of repeated administration, 37.5 ± 1.2 and 36.0 ± 1.5 ml for the pre- and postsession group, respectively.

dl-Cathinone produced dose-dependent decreases in milk intake for both pre- and postsession groups before the period of repeated drug administration (*before dose-response function*, fig. 1). Tolerance to the suppressant effects of *dl*-cathinone on milk intake developed in the presession group as shown by a shift to the right of the dose-response function determined during the period of repeated drug administration (*during dose-response function*) compared to the *before dose-response function* (fig. 1A). The ED_{50} increased 10-fold from 4.07 to 42.70 mg/kg as shown in table 1. The postsession group was more sensitive to the effects of *dl*-cathinone as indicated by a shift to the left of the *during dose-response function* (fig. 1B) with the ED_{50} halved from 2.95 to 1.51 mg/kg. There was a loss of tolerance in the presession group as indicated by a shift to the left of the dose-response function determined after the period of repeated administration (*after dose-response function*). There were no differences between the *during* and *after functions* for the postsession group.

d-Amphetamine was approximately twice as potent as *dl*-cathinone in producing dose-dependent decreases in intake of both groups (fig. 2). Furthermore, greater amounts of stereotyped behavior (*e.g.*, sniffing and head bobbing) were seen with the higher doses of *d*-amphetamine than with *dl*-cathinone. The *during dose-response function* for *d*-amphetamine was shifted to the right compared to the *before dose-response function* in the presession group (fig. 2A), indicating the development of cross-tolerance from *dl*-cathinone to *d*-amphetamine. The ED_{50} increased almost 3-fold from 1.82 to 5.13 mg/kg. In contrast, the postsession group showed an increase in sensitivity to *d*-amphetamine as indicated by a shift to the left in the *during dose-response function* (fig. 2B). The ED_{50} was reduced from 2.14 to 0.81 mg/kg. Once again, there was a loss of tolerance in the presession group as indicated by a shift to the left of the *after dose-response function*. There was no change in sensitivity between the *during* and *after dose-response functions* in the postsession group.

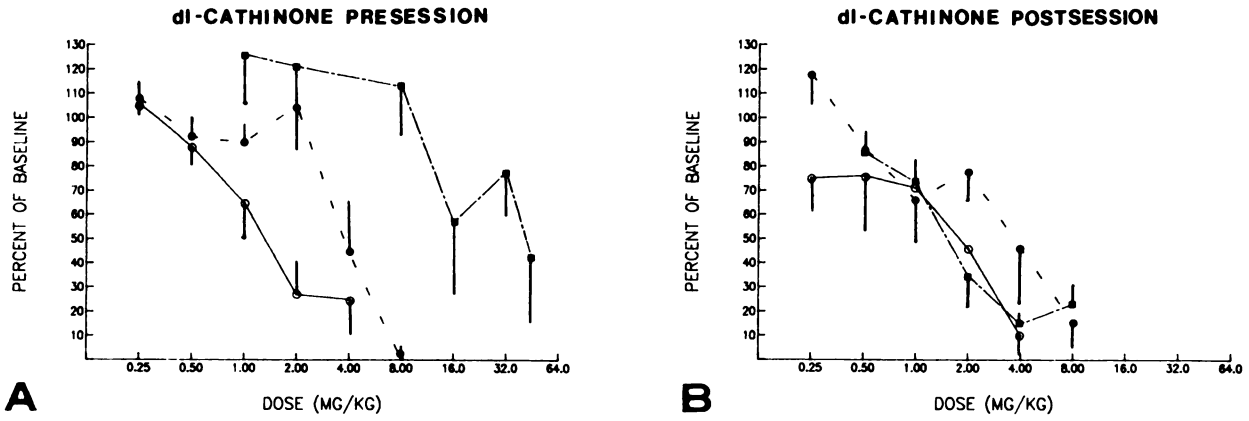

Fig. 1. Milk intake (mean and S.E.M.) as a function of dose of *dl*-cathinone for the dose-effect functions determined before (●), during (■) and after (○) a period of repeated administration of 4.0 mg/kg of *dl*-cathinone. A, animals receiving *dl*-cathinone 15 min before each session, n = 5; B, animals receiving *dl*-cathinone 15 min after each session, n = 5.

TABLE 1

ED_{50} values and 95% confidence intervals of *d*-amphetamine and *dl*-cathinone for dose-response curves determined before, during and after a period of repeated administration of *dl*-cathinone given pre- or postsession

	Before	During	After
	mg/kg	*mg/kg*	*mg/kg*
dl-Cathinone			
Pre	4.07	42.70	1.26
	(3.10-5.40)	(22.9->100)	(0.98-1.90)
Post	2.95	1.51	1.70
	(1.84-7.24)	(0.81-1.86)	(1.02-2.40)
d-Amphetamine			
Pre	1.82	5.13	0.91
	(0.81-2.57)	(3.16-17.80)	(0.50-1.44)
Post	2.14	0.81	0.96
	(1.44-3.63)	(0.56-1.05)	(0.27-4.07)

Repeated administration. Figure 3 shows the milk intake during the period of repeated administration for all rats as a function of the timing of the *dl*-cathinone injections. A dose of 4.0 mg/kg of *dl*-cathinone given before the session decreased intake to 25% of control levels on the 1st day of the repeated administration regimen. Intake in the presession group steadily increased until the 16th day when it stabilized at 70 to 80% of original levels. Over the 30 days, greater variability in intake was seen in the presession group as compared to the postsession group. The intake of the postsession group decreased slightly during the period of repeated administration to about 70% of original levels by the 20th day. The weight of the postsession group increased from 355 to 382 g during the period of repeated administration. The mean weight of the presession group was 373 g at the start of this period. This weight gradually decreased to 327 g on the 16th day but increased to 360 g before the determination of the second dose-response function.

Discussion

Single injections of *dl*-cathinone and *d*-amphetamine produced dose-dependent decreases in milk intake when administered 15 min before access to milk. In order to examine the development of tolerance to *dl*-cathinone, a dose of 4.0 mg/kg, which initially decreased milk intake to 25% of control levels, was given for a 30-day period. Half the rats received the drug before the daily session and the other half received the drug after the daily session. Tolerance developed to the suppressant effects of *dl*-cathinone on milk drinking only in rats receiving the drug before the session as evidenced by the marked shift to the right in the dose-response function for *dl*-cathinone. Cross-tolerance to *d*-amphetamine was evident as a shift to the right in the dose-response function of *d*-amphetamine. Cross-tolerance has been reported between amphetamine and a variety of other anorexigenic agents including cocaine (Woolverton *et al.*, 1978a), methylphenidate (Pearl and Seiden, 1976) and methylamphetamine (Kandel *et al.*, 1975) but not for fenfluramine (Kandel *et al.*, 1975). This indicates that cross-tolerance to amphetamine is only clearly seen with drugs that are believed to produce decreased food intake through similar neurochemical systems (Heffner and Seiden, 1979; Moore *et al.*, 1977; Scheel-Kruger, 1972).

The extent of the tolerance developed was different for the two drugs. The ED_{50} of amphetamine nearly tripled from the *before* to *during* dose-response determinations. This shift is similar in magnitude to the previously reported shifts in the dose-response functions of amphetamine-tolerant rats (MacPhail and Seiden, 1976; Pearl and Seiden, 1976; Woolverton *et al.*, 1978a). In striking contrast to the extent of tolerance to amphetamine is the 10-fold increase in the ED_{50} of cathinone during the period of repeated administration. An equivalent shift in the dose-response function of *dl*-cathinone has been reported for rats which were receiving repeated injections of *d*-amphetamine given *before* the session (Schuster and Johanson, 1980). The tolerance development to the effects of cathinone on milk intake is larger than that of any other stimulant studied to date in this procedure.

Ten days after the termination of the period of repeated administration, the dose-response functions for *dl*-cathinone and *d*-amphetamine were again determined to test for the persistence of tolerance and cross-tolerance. The dose-response functions for *d*-amphetamine and *dl*-cathinone for the presession group shifted to the left, indicating a rapid loss of tolerance. This is similar to the time course of the loss of tolerance reported for cocaine (Woolverton and Schuster, 1978), but differs from tolerance to amphetamine which has been reported to persist for 20 to 60 days (Gotestam and Lewander, 1975; MacPhail and Seiden, 1976; Schuster *et al.*, 1966; Schuster and

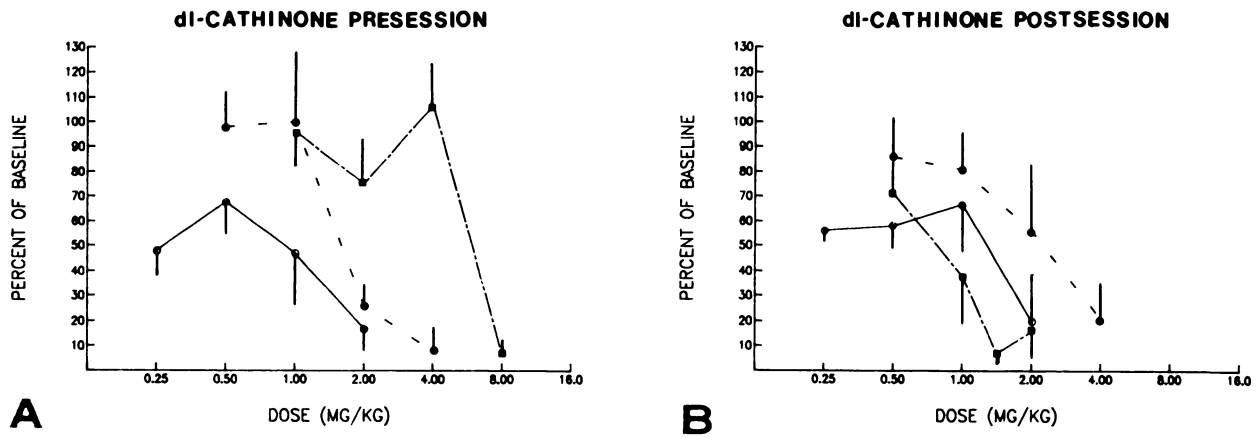

Fig. 2. Milk intake (mean and S.E.M.) as a function of dose of *d*-amphetamine for the dose-effect functions determined before (●), during (■) and after (○) a period of repeated administration of 4.0 mg/kg of *dl*-cathinone. A, animals receiving *dl*-cathinone 15 min before each session, n = 5; B, animals receiving *dl*-cathinone 15 min after each session, n = 5.

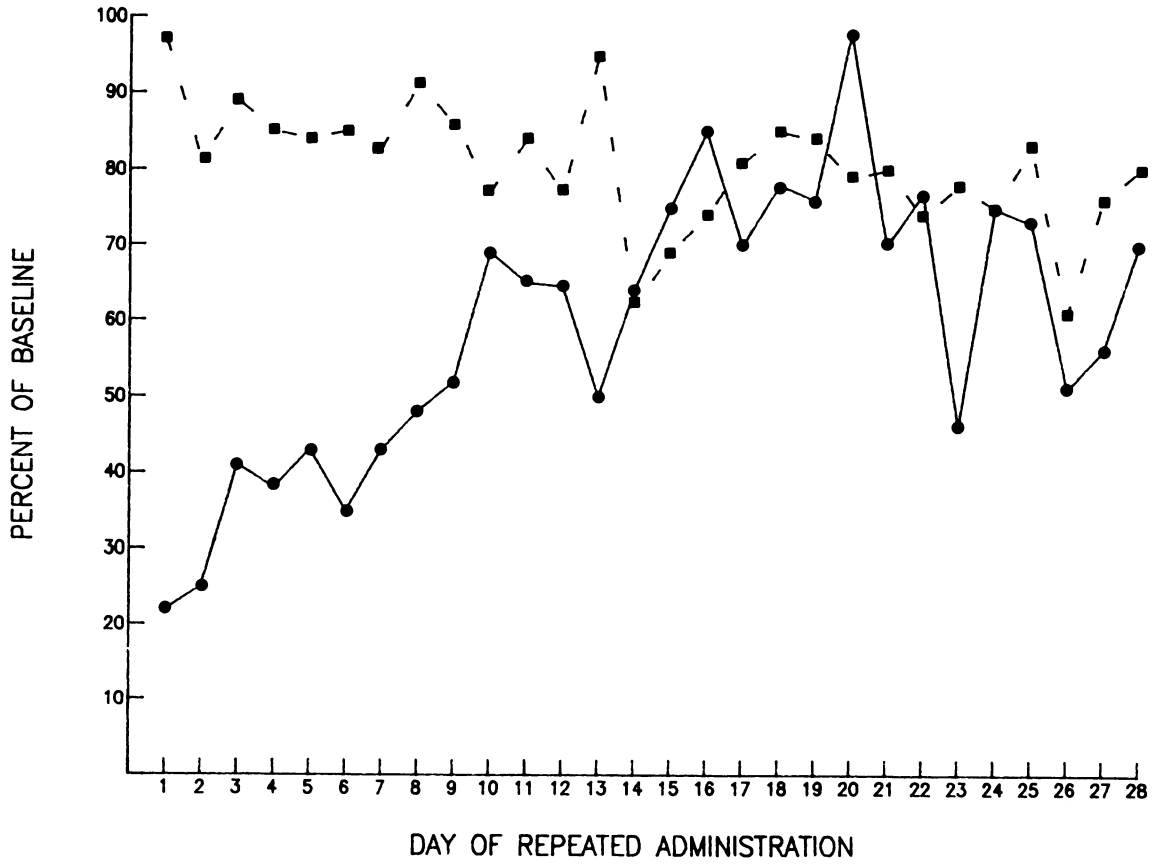

Fig. 3. Effects of repeated administration of drug or saline on mean total milk intake during the 15-min access period. The daily injections were 4.0 mg/kg of *dl*-cathinone 15 min before the session (●) and 4.0 mg/kg of *dl*-cathinone 15 min after the session (■).

Fischman, 1975). The increased sensitivity to *d*-amphetamine and *dl*-cathinone in the postsession group was still evident after the period of repeated administration. A similar increase in sensitivity to the locomotor effects of amphetamine in mice has been reported to occur for up to 16 days after a period of repeated amphetamine administration (Bailey and Jackson, 1978).

Woolverton *et al.* (1978a) reported a transient decrease in milk intake in animals receiving postsession *d*-amphetamine or cocaine during a period of repeated administration. A similar decrease is seen in the present study in rats receiving cathinone after the session. Woolverton *et al.* (1978a) suggested that administering amphetamine postsession may have resulted in the development of a gustatory avoidance response (Cappell and LeBlanc, 1978). If the presentation of a novel fluid to a rat is followed by certain events (*e.g.*, lithium chloride-induced illness), on subsequent presentations of that fluid the rat characteristically drinks less of it than the animals who had received saline. Both amphetamine (Cappell and LeBlanc, 1971; Carey, 1973) and *dl*-cathinone (Foltin and Schuster, 1981) can induce a gustatory avoidance response when administered after the presentation of a novel fluid. However pre-exposure to the fluid

(Elkins, 1973; Siegel, 1974; Vogel and Clody, 1972) or the drug (Cappell and LeBlanc, 1975; Goudie *et al.*, 1976) greatly attenuates the ability of that drug to induce a gustatory avoidance response. It is unlikely that any gustatory avoidance conditioning occurred in the animals receiving *dl*-cathinone postsession as neither the milk nor the drug were novel stimuli. The mechanism underlying the increase in sensitivity remains unknown and requires further investigation especially with respect to the time course of development and loss of supersensitivity and the possible role that environmental contingencies may have on influencing the process.

During the period of repeated administration of *dl*-cathinone, the amount of milk consumed daily by the presession group was initially decreased, but then returned to near original levels in 16 days. The time for the development of tolerance to *dl*-cathinone is similar to that for amphetamine and cocaine (4–21 days) previously reported (Carey, 1978; Carlton and Wolgin, 1971; Kandel *et al.*, 1975; Pearl and Seiden, 1976; Woolverton *et al.*, 1978b). It has been suggested that the development of tolerance to amphetamine on food intake is due to an increase in deprivation state and weight loss during the period of repeated administration (Levitsky *et al.*, 1981; Panksepp and Booth, 1973). Accordingly the mean body weight of the presession group decreased by 40 g by the 16th day of the period of repeated administration which may indicate a role for deprivation in the acquisition of tolerance. However, an increase in deprivation state cannot be the only factor as shifts in the dose-response functions were seen even though the body weight of the presession group had nearly returned to base line prior to the determination of *during dose-effect functions*. In addition, to control for any possible effects of body weight on drug effects, Pearl and Seiden (1976) maintained a group of saline control animals at decreased body weight. These animals still did not show a shift in the dose-response function as was observed in rats receiving repeated administration of *d*-amphetamine. Thus, tolerance cannot be attributed entirely to a change in deprivation level. Moreover the design of the present experiment obviates the possibility that pharmacokinetic or metabolic factors alone can account for tolerance development. Changes in absorption, distribution or metabolism should occur in animals receiving the drug after the session. The finding of tolerance development only in the presession group is more consistent with the behavioral tolerance hypothesis of Schuster *et al.* (1966). Tolerance will develop to those behavioral effects of a drug that decrease the presentation of the reinforcer. The Schuster *et al.* (1966) hypothesis was originally based on operant procedures but appears appropriate here. Although not directly measured as in the case of lever-pressing operant studies, it is obvious that a chain of operant responses is involved in the animals' drinking of milk from a dispensing tube. Thus, milk delivery may be viewed as a reinforcer for the licking response. Only the animals receiving *dl*-cathinone before the session experienced decreased milk intake (reinforcer loss) and only these animals developed tolerance during the period of repeated administration. On the other hand, animals receiving *dl*-cathinone after the session were more sensitive to the effects of both drugs in decreasing milk intake. Other experiments using postsession amphetamine have not reported increased sensitivity to the drug (Campbell and Seiden, 1973; Carlton and Wolgin, 1971; Pearl and Seiden, 1976; Schuster and Johanson, 1980). However, Woolverton *et al.* (1978a) reported increased sensitivity to *d*-amphetamine and cocaine after repeated administration of cocaine postsession using the same paradigm as used here. These authors suggested that sensitization to the effects of cocaine is the major pharmacological effect of cocaine, but environmental contingencies are capable of activating compensatory mechanisms resulting in the development of tolerance. The possible role of environmental contingencies in determining the development of tolerance or supersensitivity requires further research.

The present experiment is further evidence of the pharmacological similarities between *dl*-cathinone and *d*-amphetamine and, in addition, indicates the presence of a subtle difference between these two compounds. The similarities are demonstrated, first, by the development of tolerance to *dl*-cathinone and cross-tolerance to *d*-amphetamine only in animals having access to milk while under the influence of *dl*-cathinone during a period of repeated administration and second, by the development of supersensitivity to these drugs in animals receiving *dl*-cathinone postsession during the period of repeated administration. The difference is the much larger shift to the right of the *dl*-cathinone dose-response function in animals tolerant to *dl*-cathinone than the shift seen in the *d*-amphetamine dose-response function.

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References

Bailey, R. C. and Jackson, D. M.: A pharmacological study of changes in central nervous system receptor responsiveness after long-term dexamphetamine and apomorphine administration. Psychopharmacology **56:** 317–326, 1978.

Campbell, J. C. and Seiden, L. S.: Performance influence on the development of tolerance to amphetamine. Pharmacol. Biochem. Behav. **1:** 703–708, 1973.

Cappell, H. and LeBlanc, A. E.: Conditioned aversion to saccharin by single administrations of mescaline and *d*-amphetamine. Psychopharmacologia **22:** 352–356, 1971.

Cappell, H. and LeBlanc, A. E.: Conditioned aversion by amphetamine: Rates of acquisition and loss of the attenuating effects of prior exposure. Psychopharmacology **43:** 157–162, 1975.

Cappell, H. and LeBlanc, A. E.: Gustatory avoidance conditioning by drugs of abuse: Relationships to general issues in research on drug dependence. *In* Food Aversion Learning, ed. by N. W. Milgram, K. Krane and T. M. Alloway, pp. 133–167, Plenum Press, New York, 1978.

Carey, R. J.: Long-term aversion to a saccharin solution induced by repeated amphetamine injections. Pharmacol. Biochem. Behav. **1:** 265–270, 1973.

Carey, R. J.: A comparison of the food suppression produced by giving amphetamine as an aversion treatment versus as an anorexic treatment. Psychopharmacology **56:** 45–48, 1978.

Carlton, P. L. and Wolgin, D. L.: Contingent tolerance to the anorexigenic effects of amphetamine. Physiol. Behav. **7:** 221–223, 1971.

Elkins, R. L.: Attenuation of drug-induced bait shyness to a palatable solution as an increasing function of its availability prior to conditioning. Behav. Biol. **9:** 221–226, 1973.

Foltin, R. W. and Schuster, C. R.: The effects of *dl*-cathinone in a gustatory avoidance paradigm. Pharmacol. Biochem. Behav. **14:** 907–909, 1981.

Gotestam, K. G. and Lewander, T.: The duration of tolerance to the anorexigenic effect of amphetamine in rats. Psychopharmacologia **42:** 41–45, 1975.

Goudie, A. J., Thornton, E. W. and Wheeler, T. J.: Drug pretreatment effects in drug-induced taste aversions: Effect of dose and duration of pretreatment. Pharmacol. Biochem. Behav. **4:** 629–633, 1976.

Halbach, H.: Medical aspects of the chewing of Khat leaves. Bull. W.H.O. **47:** 21–29, 1972.

Halbach, H.: Khat—The problem today. *In* Problems of Drug Dependence, 1979, NIDA Research Monograph 27, pp. 318–319, U.S. Government Printing Office, Washington, DC, 1980.

Heffner, T. G. and Seiden, L. S.: The effect of depletion of brain dopamine by 6-hydroxydopamine on tolerance to the anorexic effect of *d*-amphetamine and fenfluramine in rats. J. Pharmacol. Exp. Ther. **208:** 134–143, 1979.

Johanson, C. E. and Schuster, C. R.: Self-administration of cathinone and its effects on schedule controlled responding in the rhesus monkey. Fed. Proc. **38:** 436, 1979.

Johanson, C. E. and Schuster, C. R.: A comparison of the behavioral effects of *l* and *dl*-cathinone, and *d*-amphetamine. J. Pharmacol. Exp. Ther. **219:** 355–362, 1981.

KALIX, P.: Hypermotility of the amphetamine type induced by a constituent of Khat leaves. Br. J. Pharmacol. **68:** 11-13, 1980a.

KALIX, P.: Hyperthermic response to (−)-cathinone, an alkaloid of *Catha edulis* (Khat). J. Pharm. Pharmacol. **32:** 662-663, 1980b.

KALIX, P.: A constituent of Khat leaves with amphetamine-like releasing properties. Eur. J. Pharmacol. **62:** 213-215, 1980c.

KALIX, P.: Cathinone, an alkaloid from Khat leaves with an amphetamine-like releasing effect. Psychopharmacology **74:** 269-270, 1981.

KANDEL, D. S., DOYLE, D. AND FISCHMAN, M. W.: Tolerance and cross-tolerance to the effects of amphetamine, methamphetamine, and fenfluramine on milk consumption in the rat. Pharmacol. Biochem. Behav. **3:** 705-707, 1975.

KNOLL, J.: Studies on the central effects of (−)-cathinone. *In* Problems of Drug Dependence, 1979, NIDA Research Monograph 27, pp. 322-323, U.S. Government Printing Office, Washington, DC, 1980.

LEVITSKY, D. A., STRUPP, B. J. AND LUPOLI, J.: Tolerance to anorectic drugs: Pharmacological or artifactual. Pharmacol. Biochem. Behav. **14:** 661-667, 1981.

LUQMAN, W. AND DANOWSKI, T. S.: The use of Khat (*Catha edulis*) in Yemen: Social and medical observations. Ann. Intern. Med. **85:** 246-249, 1976.

MACPHAIL, R. C. AND SEIDEN, L. S.: Effects of intermittent and repeated administration of *d*-amphetamine on restricted water intake in rats. J. Pharmacol. Exp. Ther. **197:** 303-310, 1976.

MOORE, K. E., CHIEUH, C. E. AND ZELDES, G.: Release of neurotransmitters from the brain *in vivo* by amphetamine, methylphenidate and cocaine. *In* Cocaine and Other Stimulants, ed. by E. H. Ellinwood and M. M. Kilbey, pp. 143-160, Plenum Press, New York, 1977.

PANKSEPP, J. AND BOOTH, D. A.: Tolerance to the depression of intake when amphetamine is added to the rat's food. Psychopharmacologia **29:** 45-54, 1973.

PEARL, R. AND SEIDEN, L. S.: The existence of tolerance to and cross-tolerance between *d*-amphetamine and methylphenidate for their effects on milk consumption and on differential-reinforcement-of-low-rate performance in the rat. J. Pharmacol. Exp. Ther. **198:** 636-647, 1976.

ROSECRANS, J. A., CAMPBELL, O. L., DEWEY, W. L. AND HARRIS, L. S.: Discriminative stimulus and neurochemical mechanism of cathinone: A preliminary study. *In* Problems of Drug Dependence, 1979, NIDA Research Monograph 27, pp. 328-329, U.S. Government Printing Office, Washington, DC, 1980.

SCHEEL-KRUGER, J.: Behavioral and biochemical comparisons of amphetamine derivatives, cocaine, benztropine, and tricyclic antidepressant drugs. Eur. J. Pharmacol. **18:** 63-73, 1972.

SCHUSTER, C. R., DOCKENS, W. S. AND WOODS, J. H.: Behavioral variables affecting the development of amphetamine tolerance. Psychopharmacologia **9:** 170-182, 1966.

SCHUSTER, C. R. AND FISCHMAN, M. W.: Amphetamine toxicity: Behavioral and neuropathological indexes. Fed. Proc. **34:** 1845-1851, 1975.

SCHUSTER, C. R. AND JOHANSON, C. E.: Behavioral studies of cathinone in monkeys and rats. *In* Problems of Drug Dependence, 1979, pp. 324-325, NIDA Research Monograph 27, U.S. Government Printing Office, Washington, DC, 1980.

SIEGEL, S.: Flavor aversion and "learned safety." J. Comp. Physiol. Psychol. **87:** 1073-1082, 1974.

VOGEL, J. R. AND CLODY, D. E.: Habituation and conditioned food aversion. Psychon. Sci. Animal Physiol. Psychol. **28:** 275-276, 1972.

WOOLVERTON, W. L., KANDEL, D. AND SCHUSTER, C. R.: Tolerance and cross-tolerance to cocaine and *d*-amphetamine. J. Pharmacol. Exp. Ther. **205:** 525-535, 1978a.

WOOLVERTON, W. L., KANDEL D. AND SCHUSTER, C. R.: Effects of repeated administration of cocaine on schedule-controlled behavior of rats. Pharmacol. Biochem. Behav. **9:** 327-337, 1978b.

WOOLVERTON, W. L. AND SCHUSTER, C. R.: Behavioral tolerance to cocaine. *In* Behavioral Tolerance: Research and Treatment Implications, NIDA Research Monograph 18, pp. 127-141, U.S. Government Printing Office, Washington, DC, 1978.

YANAGITA, T.: Studies on cathinones: Cardiovascular and behavioral effects in rats and self-administration experiments in rhesus monkeys. *In* Problems of Drug Dependence, 1979, NIDA Research Monograph 27, pp. 326-327, U.S. Government Printing Office, Washington, DC, 1980.

ZELGER, J. L. AND CARLINI, E. A.: Anorexigenic effects of two amines obtained from *Catha edulis* Forsk (Khat) in rats. Pharmacol. Biochem. Behav. **12:** 701-705, 1980.

ZELGER, J. L., SCHORNO, HJ. X. AND CARLINI, E. A.: Behavioral effects of cathinone, an amine obtained from *Catha edulis* Forsk: Comparisons with amphetamine, norpseudoephedrine, apomorphine and nomifensine. Bull. Narc. **32:** 67-81, 1980.

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