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The puzzle of drug-induced conditioned taste aversion: Comparative studies with cathinone and amphetamine*

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Abstract. The potency of *dl*-cathinone (the active constituent of the Khat plant) was compared with that of *d*-amphetamine in the conditioned taste aversion (C.T.A.) procedure and in a test of drug-induced adipsia in rats. Both drugs induced C.T.A., the potency ratio being 1:17 (amphetamine was more potent). Both drugs induced adipsia in deprived rats given access to water for 120 min. The potency ratio in this procedure was 1:4. Potency in the C.T.A. procedure did not therefore correlate with potency in inducing adipsia; consequently drug-induced C.T.A. cannot be attributed to conditioned adipsia. In the adipsia test the drugs had similar durations of action, thus factors related to duration of drug action (cf Cappell and Le Blanc 1977) cannot account for the surprisingly low potency of cathinone in the C.T.A. procedure. These data, obtained with stimulant drugs with similar structures and similar actions in a variety of conventional in vivo and in vitro pharmacological tests, illustrate the unpredictable nature of drug actions in the C.T.A. procedure. The low potency of cathinone in inducing C.T.A. could not be predicted from knowledge of the potency of this compound in tests of adipsia (as shown here) or (as reported elsewhere) in tests of anorexia, locomotor stimulation, stereotypy, suppression of operant responding, drug discrimination, release and inhibition of reuptake of dopamine and noradrenaline, lethality and actions on the cardiovascular system. All of these studies have reported potency ratios considerably lower than 1:17, which were nevertheless similar to the 1:4 ratio observed in the adipsia test. It is suggested that the weak potency of cathinone in the C.T.A. procedure *may* be related to its comparatively potent reinforcing actions in the self-administration procedure.

Key words: Khat – Cathinone – Amphetamine – Conditioned taste aversion – Adipsia – Toxicity – Self-administration – Rat

The fresh leaves of the Khat plant are chewed in a range of third world countries (Krikorian 1983), the major reason for Khat intake being the euphoria and hyperactivity that follows ingestion (Hallbach 1972). The main active constituent of Khat is now generally believed (Szendrei 1983) to be cathinone (α-aminopropiophenone), which is a phenylethylamine derivative structurally closely related to amphetamine (Zelger et al. 1979). In a variety of in vivo and in vitro tests, cathinone's actions are very similar to those of amphetamine (Kalix 1984a; Khan and Kalix 1984 for reviews). Cathinone and amphetamine are therefore structurally related compounds with very similar actions, both being indirect peripheral sympathomimetics and central stimulants.

However, Foltin and Schuster (1981) suggested that the potency of cathinone in the conditioned taste aversion (C.T.A.) paradigm was lower than would be expected on the basis of its similarity to amphetamine. In the C.T.A. paradigm, ingestion of a novel tasting food or fluid is followed by drug treatment. Following recovery, most drugs are found to induce an aversion for the "target" food or fluid (Goudie 1979). This conditioned aversion is typically *assumed* to be due to drug-induced "malaise" or to other aversive stimulus properties of the drug studied. The factors mediating drug-induced C.T.A. remain unclear (Stolerman and D'Mello 1981). One strategy for analysing drug actions in this procedure is to compare the effects of closely related compounds, so that specific pharmacological or behavioural effects can be correlated with actions in the C.T.A. procedure (Booth et al. 1977; Switzman et al. 1981). To date, attempts to analyse the mechanisms involved in drug-induced C.T.A. using this strategy have not been successful (Goudie 1985a). However, Foltin and Schuster's (1981) brief report on the low potency of cathinone in inducing C.T.A. suggested that a further attempt at such an analysis might be fruitful, particularly with two compounds with such closely related structure and pharmacology as amphetamine and cathinone. We therefore conducted a detailed comparison of the actions of cathinone and amphetamine in the C.T.A. procedure. Initially, we were concerned with determining whether cathinone does actually have low potency in inducing C.T.A., since Foltin and Schuster's (1981) report suffers from two limitations. Firstly, they only investigated the actions of cathinone in inducing C.T.A.; they did not study subjects receiving amphetamine (or any other reference drug). In the C.T.A. procedure drug actions are modified by numerous methodological factors; a direct comparison between cathinone and amphetamine in an experiment involving a standardised procedure in one strain of rats therefore seems essential (cf Foltin and Schuster

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1982b). Secondly, Foltin and Schuster's (1981) study was not designed to detect C.T.A. with the most sensitive procedures available. Two-bottle tests are the most sensitive indices of C.T.A. (Grote and Brown 1971), and therefore the threshold dose of cathinone that produced a significant aversion in Foltin and Schuster's (1981) study (16.0 mg/kg) may have underestimated cathinone's potency due to the absence of choice tests.

The experiments reported here replicate and extend Foltin and Schuster's (1981) study. The first experiment studied C.T.A. induced by amphetamine and cathinone, allowing an estimate to be obtained of cathinone's relative potency. In this study, a two-bottle test was administered after multiple one-bottle conditioning trials to provide a highly sensitive assay for C.T.A. (cf Booth et al. 1977). In the second experiment, the relative potency of cathinone and amphetamine in inducing adipsia was determined to assess whether the relative potency of cathinone in inducing C.T.A. was similar to the relative potency of the drug in inducing adipsia. This allowed a test of the hypothesis (Carey 1978) that drug-induced C.T.A. is due to taste-mediated conditioned adipsia. In this second study we also compared the durations of action of cathinone and amphetamine in inducing adipsia by recording water intake at various times after drug injection. This allowed us to test the hypothesis (e.g. Cappell and Le Blanc 1977) that factors related to duration of drug action determine the potency of drugs in the C.T.A. procedure.

Materials and methods

Experiment 1: Conditioned taste aversion

Animals. Fifty-six female Lister hooded rats (200–300 g) were individually housed in a temperature- ($23 \pm 2°$ C) and light- (12 h cycle) controlled room. Food was freely available. Water was given on a regime described below.

Procedure. Subjects were randomly assigned to seven groups ($n = 8$). On conditioning trials three groups received *dl*-cathinone at 1, 4 and 16 mg/kg respectively; three groups received *d*-amphetamine at 0.25, 0.5 and 1.0 mg/kg and one group acted as an injection control. All animals received water for 20 min/day on Mondays through Fridays, and for 1 h on Saturdays and Sundays. Conditioning trials were always conducted on Fridays. Baseline water intakes were measured on Thursdays, prior to conditioning trials on Fridays when subjects received 0.1% sodium saccharin solution for 20 min when 23 $^2/_3$ h deprived. Injections were administered within 20 min of saccharin access. Amounts of fluid consumed were recorded by weighing water bottles to the nearest 0.1 g. Subjects were initially adapted to the regime of restricted water access for 10 days, starting on a Monday. Measurement of baseline water intake took place on Day 11 (a Thursday). The first conditioning trial took place on Day 12 (a Friday). Baseline water intake measurements were taken on Days 18, 25, and 32 before conditioning trials on Days 19, 26, and 33. Thus all animals received four one-bottle conditioning trials, each preceded by measurement of the baseline level of water intake on the previous day. Subsequent to the conditioning trials, subjects were maintained on the restricted water access regime for a further week. On Day 40, subjects received a two-bottle choice test between water and 0.1% saccharin, which involved placing 23 $^2/_3$ h water-deprived rats in a cage with both water and saccharin available for 20 min. The location of water and saccharin bottles was counterbalanced, and amounts consumed by each animal were recorded to the nearest 0.1 g. The procedure of four one-bottle conditioning trials followed by a single two-bottle test provides a highly sensitive test for C.T.A. (Booth et al. 1977) because multiple conditioning trials increase the magnitude of conditioning effects and two-bottle tests are more sensitive tests for C.T.A. than single-bottle tests (Grote and Brown 1971).

Drugs. dl-Cathinone oxalate (α-aminopropiophenone) was supplied by Dr. Hsj. X. Schorno (Cantonal Hospital, 6004 Lucerne, Switzerland). *d*-Amphetamine sulphate was a gift from Smith, Kline and French (Welwyn Garden City, England). Drugs were dissolved in 0.9% saline and doses calculated as salts. Injections were IP at 2 ml/kg. Doses were based on previous reports of the potency of cathinone (Foltin and Schuster 1981) and amphetamine (D'Mello et al. 1977) in the C.T.A. procedure.

Experiment 2: Drug-induced adipsia

Animals. Subjects were 56 female hooded rats (180–275 g), housed as described above.

Procedure. There were seven groups of subjects ($n = 8$ per group), corresponding to the groups in Experiment 1. Subjects were initially adapted for 5 days (Monday–Friday) to a regime of 20 min water access per day when 23 $^2/_3$ h deprived. On the following Saturday and Sunday, subjects received 1 h of water access/day. On the following Monday, subjects were returned for 3 days to the 20 min/day regime. On the Thursday of the same week, after 10 days of restricted access, half the subjects in each group received drug treatment prior to water access for 120 min. The remaining subjects received the relevant treatment on the following day (Friday). Baseline levels of water intake (in 20 min) were recorded on the days prior to drug treatment (i.e. on the Wednesday and Thursday for each half of the subjects). Drugs were administered 30 min before water access, and doses were made up as described for the seven groups in the C.T.A. study. Fluid intake was recorded by weighing water bottles to the nearest 0.1 g at the start of the access period and 30, 60 and 120 min later.

Statistics (Experiments 1 and 2). Fluid intake data were analysed with ANOVAs and Tukey HSD multiple comparison tests. Log dose/response curves were analysed with least squares log-linear regression techniques. *Only* the sensibly linear portions of each log dose/response curve were analysed in this way to avoid the data being confounded by "floor" effects. Percentage preference scores were subjected to arc-sine transform prior to analysis.

Results

Experiment 1: Conditioned taste aversion

Water intakes recorded on the Thursdays preceding each conditioning trial were analysed with a two-factor ANOVA (groups, days) with repeated measures over days. There was no main effect of groups ($F = 1.55$, $df = 6, 48$, $P > 0.05$),

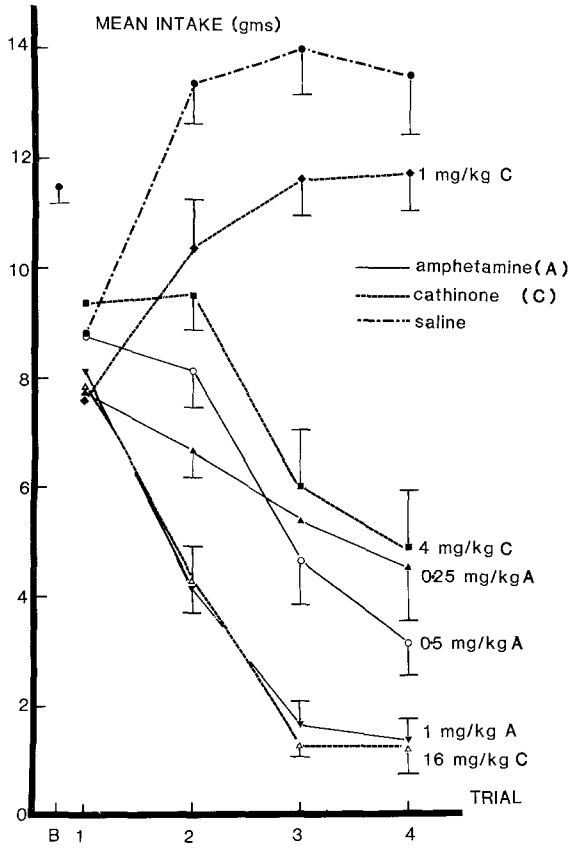

Fig. 1. Mean (±SE) amounts (g) of saccharin consumed by each of seven experimental groups over four successive periods of saccharin access. Also shown at B is the baseline level of water intake (for all subjects) on Day 11 immediately prior to the first conditioning trial. Following each conditioning trial subjects were injected with saline (one group) amphetamine (three groups) or cathinone (three groups). Some SEs have been left out of the figure for sake of clarity

Table 1. Calculated AD_{50} values (mg/kg) for each drug on each trial. Also shown are the potency ratios obtained on each trial

	Cathinone	Amphetamine	Potency ratio Amphetamine:Cathinone
Trial 2	13.33	0.76	1:17.54
Trial 3	3.51	0.20	1:17.55
Trial 4	3.13	0.19	1:16.47

Note that the AD_{50} value for each drug decreases progressively though Trials 2–4. This effect is due to the cumulative consequence of repeated conditioning Trials (e.g. the AD_{50} calculated on Trial 4 is a *consequence* of conditioning on Trials 1 through 3)

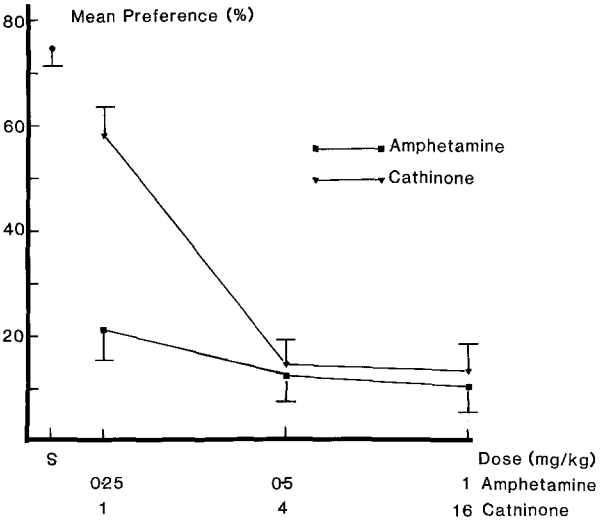

Fig. 2. Mean (±SE) saccharin preference scores (percentages) in the two-bottle test as a function of dose of cathinone or amphetamine. Also shown (at *S*) are the data from the saline control group. Drug doses are plotted on logarithmic scales

nor was there a significant interaction ($F<1$); thus all groups were equated for baseline water intake on all days before conditioning trials. Figure 1 shows the saccharin consumption for each group over the four successive periods of saccharin access.

On first access to saccharin (trial 1) subjects drank less than on the previous day when water intake was recorded. The overall mean (±SE) saccharin intake was 8.46±0.27 g, while the mean baseline water intake was 11.44±0.29 g. This reduction in fluid intake was significant (matched $t=$ 7.55, $P<0.01$). This effect is due to neophobia induced by the novel tasting fluid. After repeated access to saccharin neophobia dissipates (cf Goudie et al. 1978) and saccharin intake in controls increases above baseline water intake. As shown in Fig. 1, all drug-treated groups showed absolute reductions in intake over trials except the 1 mg/kg cathinone group. Both drugs induced clear dose-dependent C.T.A.

To make potency comparisons between the two drugs, regression analyses were applied to the log dose/response data obtained from *each* of conditioning trials 2, 3 and 4. Such analyses were conducted only on the sensibly linear portion of the dose/response curve for each trial. After multiple trials it was clear (Fig. 1) that "floor" effects were observed with both drugs at some doses. Thus data points obtained with different doses were used in calculating the regression lines for the various trials in order to utilise only data from the linear portion of each dose/response curve, thus avoiding the data being confounded by "floor" effects. To compare the potency of the drugs, a statistic termed the AD_{50} (the dose which reduced saccharin intake to the level of 50% of the control group on each trial) was estimated for each drug on each trial from the calculated regression lines. The estimated AD_{50} values are shown in Table 1, as are the potency ratios obtained for the drugs on each trial.

Figure 1 shows that, over all conditioning trials, amphetamine at 0.25 mg/kg suppressed saccharin intake to an extent approximately equal to that induced by 4.0 mg/kg cathinone (i.e. 16 times greater). Likewise, over all conditioning trials, the effects of a dose of 1 mg/kg amphetamine resembled those of cathinone at 16.0 mg/kg. The calculated potency ratios of 1:16 or 17 clearly provide valid and accurate measures for these data.

The results of the two-bottle preference test are shown in Fig. 2. The "floor" effects observed in the two-bottle test prevented these data being utilised to compare the potency of the two drugs. Single factor (dose) ANOVAs were calculated for the preference scores from subjects receiving treatment with cathinone and amphetamine respectively, the saline control group (0 mg/kg dose) being included in both ANOVAs. For cathinone there was a significant effect

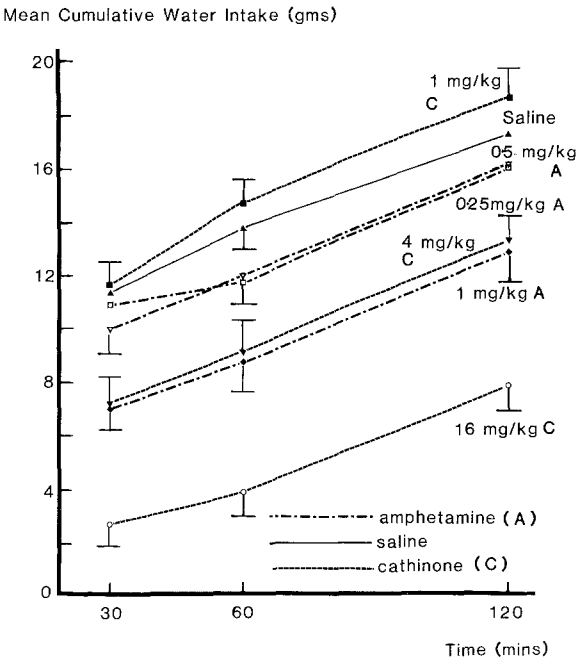

Fig. 3. Mean (±SE) cumulative water intakes for each of seven experimental groups as a function of time of exposure to water (over a 2-h period) in deprived subjects. Three groups of subjects were treated with cathinone, three with amphetamine and one with saline

of dose ($F=31.87$, $df=3$, 28, $P<0.01$), as there was for amphetamine ($F=23.52$, $df=3$, 28, $P<0.01$). For subsequent multiple comparison tests α was set at the 0.01 level to eliminate any possibility of false positive errors. For cathinone-treated subjects, significant differences were found for comparisons of saline vs 4.0 mg/kg; saline vs 16.0 mg/kg; 1.0 mg/kg vs 4.0 mg/kg and 1.0 mg/kg vs 16.0 mg/kg. Thus cathinone produced dose-related C.T.A. with a "floor" effect at 4.0 mg/kg and a significant C.T.A. relative to controls (with a conservative test) at doses of 4.0 and 16.0 mg/kg. For amphetamine-treated subjects, significant differences were found for comparisons of saline versus all drug doses. No differences were found between groups receiving different doses of amphetamine. A potent C.T.A. was produced by all doses of *d*-amphetamine, with a "floor" effect confounding the observation of a dose/response relationship.

In summary, significant C.T.A. was produced by all doses of *d*-amphetamine but only by 4.0 and 16.0 mg/kg *dl*-cathinone. Potency comparisons between the compounds indicated that *d*-amphetamine was 16–17 times more potent.

Experiment 2: Drug-induced adipsia

Baseline levels of water intake (data not shown) did not differ between the groups on the days preceding adipsia tests ($F=1.56$, $df=6$, 49, $P>0.05$). All groups were therefore in equivalent motivational states prior to the adipsia tests. The effects of the various drug treatments on water intake over the 2-h experimental period are shown in Fig. 3, which shows that each drug had clear dose- and time-related adipsic effects.

Comparison of the intake of the saline control group with that of the 1.0 mg/kg *d*-amphetamine group revealed that a significant adipsic effect was seen at all three sampling periods (smallest $t=3.33$, $df=14$, $P<0.01$, two tailed). Similarly, 16.0 mg/kg cathinone induced significant adipsia at all three time periods (smallest $t=8.03$, $df=14$, $P<0.001$). Figure 3 indicates clearly that 1.0 mg/kg amphetamine was equipotent to 4.0 mg/kg cathinone in inducing adipsia at all time periods, i.e. these equipotent doses had equivalent durations of action. The effects of these two equipotent doses were compared with *t* tests which indicated that at no time was there a significant difference between the groups receiving 4.0 mg/kg cathinone and 1.0 mg/kg amphetamine (largest $t=0.21$, $df=14$), confirming the equal potency of these doses and their equivalent durations of action.

In summary, these data indicate that *d*-amphetamine was approximately 4 times as potent as *dl*-cathinone in causing adipsia. Furthermore, equipotent doses of the two drugs had equivalent durations of action.

Discussion

Direct comparisons in the same laboratory between cathinone and amphetamine in inducing C.T.A. and adipsia demonstrated clearly the surprisingly low potency of cathinone in the C.T.A. procedure, in support of Foltin and Schuster's (1981) preliminary findings. The need for a series of experiments comparing the actions of cathinone with another drug is highlighted by the fact that with cocaine, which is also a weak C.T.A.-inducing agent, discrepant findings have been obtained in C.T.A. studies (Goudie et al. 1978; D'Mello et al. 1981; Cappell and Le Blanc 1977; Foltin and Schuster 1982b). Foltin and Schuster's (1981) report on the low potency of cathinone in the C.T.A. procedure *might* therefore have simply been "atypical" due to the action of (unknown) factors which modify the potency of drugs in the C.T.A. procedure. The potency of *dl*-cathinone in inducing C.T.A. was only 1/17th that of *d*-amphetamine; in contrast, its relative potency in inducing adipsia was 1:4. The C.T.A.-inducing properties of the compounds do not therefore correlate with their adipsic actions and C.T.A. cannot be attributed to conditioned adipsia (Carey 1978), in agreement with previous conclusions of Stolerman and D'Mello (1978).

The potency of *dl*-cathinone relative to *d*-amphetamine has previously been compared in various tests in this laboratory with our strain of rats. The ratio of *dl*-cathinone to *d*-amphetamine was 1:3 for suppression of operant responding (Goudie 1985b) and 1:2 in the drug discrimination procedure (Goudie et al. 1984). These ratios resemble that reported above for the adipsia test, but differ markedly from the 1:17 ratio reported for the C.T.A. procedure. Other reports have indicated that the potency ratio of *dl*-cathinone to *d*-amphetamine is between 1:1 and 1:4 for tests of drug-induced anorexia (Foltin and Schuster 1982a), lethality (Huang and Wilson 1983), locomotor stimulation and stereotypy (Zelger et al. 1979), drug discrimination (Schechter et al. 1984) and effects on operant behaviour (Johanson and Schuster 1981). A number of studies have compared the potency of *d*-amphetamine with *l*-cathinone (as opposed to *dl*-cathinone). These studies have *also* typically generated ratios between 1:1 and 1:4 in a range of tests, including motor stimulation (Kalix 1980a), anorexia (Foltin et al. 1983), drug discrimination (De La Garza and Johanson 1983), actions on the cardiovascular system

(Kohli and Goldberg 1982), and in vitro actions on serotonin, dopamine and noradrenaline release and reuptake (Kalix 1980b, 1981, 1982, 1983a, 1983b, 1984b). Potency ratios derived from studies with *l*-cathinone should be compared with some caution with ratios derived from studies (such as those reported above) conducted with *dl*-cathinone. Nevertheless, it is obvious that the 1:17 ratio obtained in our C.T.A. study differs markedly from the results of *all* studies in which amphetamine has been compared to cathinone. The low potency of cathinone in the C.T.A. procedure clearly could not have been predicted on the basis of *any* previous reports of cathinone's pharmacology; other than, of course, the prior brief C.T.A. study of Foltin and Schuster (1981). Thus the enigmatic nature of C.T.A. is highlighted by our data, which resemble previous studies which have failed to detect specific pharmacological or behavioural actions which can be correlated with potency in the C.T.A. procedure (Booth et al. 1977; Stolerman and D'Mello 1978; Greenshaw and Dourish 1984a, b; Switzman et al. 1981), although our data differ somewhat from these reports in that we have studied two compounds with *very* similar structures, pharmacological actions and pharmacokinetics.

One factor which has consistently been implicated as a determinant of the potency of drugs in the C.T.A. procedure is duration of drug action (Goudie et al. 1978; Goudie and Thornton 1977; Goudie and Dickins 1978; Cappell and Le Blanc 1977; Domjan et al. 1981; Foltin and Schuster 1982b). Systematic tests of this hypothesis have not always generated supportive data (D'Mello et al. 1981; Greenshaw and Dourish 1984b) and its validity is not at present clear (Goudie 1985a). Nevertheless, the hypothesis continues to be influential in attempts to predict the potency of drugs in the C.T.A. procedure (see e.g. Riley and Tuck 1985). The data reported here are, however, not in accord with the hypothesis, since cathinone and amphetamine had equivalent durations of action in inducing adipsia. Other studies have also reported that cathinone and amphetamine have similar durations of actions in a variety of procedures (Zelger et al. 1979; Zelger and Carlini 1980; Glennon and Showalter 1981; Goudie 1985b). The hypothesis that duration of action is a critical determinant of the potency of drug actions in the C.T.A. procedure therefore clearly cannot account for the data reported here.

Finally, it is tempting to speculate on the basis of the data reported here that the actions of drugs in the C.T.A. procedure may be related to their self-administration potential. Cathinone resembles cocaine in that both compounds are highly potent reinforcing agents (Woolverton and Johanson 1984) and both possess weak aversive properties. Thus cathinone resembles cocaine rather than amphetamine, which has potent aversive actions. It is possible that low potency in the C.T.A. procedure may, all other things being equal, predispose drugs to high potency in the self-administration procedure. However, a very considerable body of empirical research will clearly be required to validate or refute this hypothesis.

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