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Comparative Effects of Cathinone and Amphetamine on Fixed-Interval Operant Responding: A Rate-Dependency Analysis

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GOUDIE, A. J. *Comparative effects of cathinone and amphetamine on fixed-interval operant responding: A rate-dependency analysis.* PHARMACOL BIOCHEM BEHAV **23**(3) 355–365, 1985.—The actions of dl-cathinone and d-amphetamine on operant responding were compared in rats. The effects of both drugs were predominantly suppressive on behaviour maintained by a Fixed Interval 2 minutes schedule of reward. Both drugs had equivalent durations of action in suppressing responding. The actions of the two compounds could be described as rate-dependent, although their rate-dependent actions could most parsimoniously be attributed to drug-induced rate constancy. Methysergide (10 mg/kg) had no significant differential effect on the response suppressant effects of the two compounds, even though in vitro studies have indicated that cathinone and amphetamine differ in their serotonin receptor affinity. The actions of cathinone were qualitatively similar to those of amphetamine in this behavioural test. Furthermore the observed potency ratio for dl-cathinone to d-amphetamine (1:3) was similar to that reported elsewhere in a range of other behavioural tests (anorexia, adipsia, drug-induced rotation, lethality) for this pair of isomers. The only major difference reported to date between the behavioural actions of cathinone and amphetamine relates to the unexpectedly weak potency of cathinone in the conditioned taste aversion procedure. Cathinone, the major active constituent of the Khat plant, is therefore a psychostimulant drug which may possess potent reinforcing properties by virtue of its amphetamine-like stimulant actions coupled with its very weak aversive properties.

Khat Cathinone Amphetamine Operant behaviour Methysergide Rate-dependency Fixed interval schedule Taste aversion Rats

KHAT (Catha edulis Forsk) is a perennial shrub indigenous to East and Southern Africa and Arabia which has been used for centuries as a medicinal agent in various cultures (see [34] for a detailed review). The fresh, or more rarely, dried leaves of Khat are chewed or consumed as a tea for their pharmacological effects, which include a phenylethylamine-like stimulant action [3,20]. Khat is a complex plant with a range of pharmacologically active constituents some of which are not of the phenylethylamine type [46]. However, it is generally believed that the psychostimulant actions of Khat are important in determining its widespread use in a variety of cultures. This use has important socio-economic [45], medical [49], and legal implications.

For many years the stimulant effects of Khat were attributed to cathine (norpseudoephedrine) a phenylethylamine derived compound found in the plant [1]. However, the tendency for Khat users to ingest only the freshest leaves of the plant [3] suggested that an active precursor for cathine, which is rapidly degraded, might exist in the Khat plant [20]. Subsequent analysis resulted in the isolation of an active phenylethylamine derivative, alpha-aminopropiophenone [43]. This compound is now generally termed cathinone. Cathinone has the same structure as amphetamine except for a keto substitution on the beta carbon atom of the amine side chain [53]. In a range of studies cathinone has been shown to be more potent in its actions than cathine [14, 28, 45, 49, 52, 53], and it is therefore now considered to be the major active constituent of the Khat plant. Cathinone is therefore a compound that is of interest as a psychoactive agent in its own right, from the point of view of the ethno-pharmacologist, and because of the significant medical and socio-economic consequences of Khat use.

In a variety of in vivo and in vitro pharmacological tests cathinone and amphetamine have been reported to have very similar actions. Cathinone has similar effects to amphetamine on operant behaviours [22,51]. Furthermore, both drugs induce motor stimulation at low doses [14, 24, 47, 54] and stereotypy at higher doses [54]. Both compounds have anorectic properties [9, 10, 11, 53], and they show anorectic cross-tolerance [9]. Both drugs are self-administered by monkeys [50] and rats [51]. They also possess similar discriminative stimulus properties in monkeys [6] and rats [19, 41, 42], and both compounds are effective in producing conditioned taste aversions [8,19]. In rats with unilateral lesions of the substantia nigra both cathinone and amphetamine induce ipsilateral turning, suggesting that they have indirect dopamine releasing actions [52], a conclusion confirmed by in vitro findings [23, 26, 27], which demonstrate that both agents also block dopamine reuptake [48,52] and facilitate noradrenaline release [28, 29, 32]. Furthermore, following chronic treatment cathinone, like amphetamine, has

neurotoxic actions on dopaminergic areas of the brain [48]. Cathinone and amphetamine have similar EEG effects [2], both induce lipolysis [38] and hyperthermia [25], and have very similar cardiovascular effects—causing increases in heart rate and blood pressure [33]. Cathinone is clearly an indirectly acting peripheral sympathomimetic and central stimulant agent which shares many of amphetamine's properties. Furthermore, some data indicate that excessive consumption of Khat leaves can lead to a toxic psychosis similar to that seen following chronic amphetamine usage [12], although this is believed to be a rare phenomenon [20,30].

However, despite the fact that cathinone and amphetamine have similar structure and share many pharmacological actions, some reports indicate that the actions of these two compounds may differ in significant ways. For example, in conditioned taste aversion studies, the potency of cathinone is considerably weaker than would be predicted on the basis of its similarity to amphetamine [8,19]. Furthermore, the toxic (lethal) effects of the two drugs can be neurochemically dissociated, the LD_{50} of amphetamine is reduced by haloperidol pretreatment which has no effect on the LD_{50} of cathinone [21]. However, cathinone toxicity is potentiated by methysergide pretreatment at doses which have no effect on amphetamine's LD_{50} [21]. These data are suggestive of a differential action of cathinone and amphetamine on serotoninergic systems, and indeed in vitro studies with the rat fundus preparation indicate that dl-cathinone has twice the 5HT receptor affinity of dl-amphetamine [15]. Drug discrimination studies also suggest that cathinone and amphetamine have differential effects on 5HT systems, since cathinone generalizes to quipazine, a putative 5HT agonist, to a much greater extent than amphetamine [13].

Only a single full report has been published to date on the comparative actions of cathinone and amphetamine on operant responding [22]. This was conducted in monkeys; and demonstrated that although the two drugs had similar actions in suppressing operant responding, it appeared that the two compounds had different durations of action, cathinone being shorter acting. Conventional rate-dependency analyses [7] indicated that unequivocal evidence for rate-dependent effects of cathinone was not forthcoming. As part of a larger body of experiments [19] aimed at comparing the pharmacological actions of cathinone and amphetamine, we have therefore conducted a systematic comparison of the effects of cathinone and amphetamine on behaviour maintained by a Fixed Interval schedule of food reward in rats. This procedure allowed us to assess the rate-dependent actions of both agents. The effects of cathinone and amphetamine were assessed in the presence and absence of the 5HT receptor blocker methysergide in an attempt to determine whether cathinone and d-amphetamine's *behavioural* actions are differentially susceptible to neurochemical manipulations which modify the actions of 5HT systems, as might be predicted from the in vitro report of the differential affinity of these compounds for 5HT receptors [15]. Furthermore, we have conducted a parametric study to determine whether or not cathinone and amphetamine have different durations of action on operant behaviour as has been suggested [22].

Data on the comparative duration of action of d-amphetamine and cathinone is of particular interest in the light of a recent report which indicates that cathinone is a highly potent reinforcing agent in comparison to other psychostimulants [50]. Cathinone also has remarkably weak aversive properties in the conditioned taste aversion (C.T.A.) procedure [8,19], and it is possible that low potency in the C.T.A. procedure *may* be correlated with high potency in the self-administration procedure. Furthermore, both these effects might be attributable, in part, to cathinone having a comparatively short duration of action [17]. Thus the duration of action data reported here allow an evaluation of the hypothetical pharmacokinetic account [17] of the factors affecting the potency of closely related drugs in the taste aversion and self-administration procedures.

METHOD

Subjects

Eight naive male Lister hooded rats were maintained at approximately 80% of their ad lib body weights (between 300 and 380 g) by restricted daily feeding. Subjects were derived from the breeding stock of the Liverpool University Psychology Department. They were individually housed in a temperature controlled room (21 ± 2°C). Water was available ad lib. Behavioural testing always occurred at the same time daily, between 0900 and 1300 hr.

Apparatus

Standard operant chambers (Colbourn Instruments Inc. U.S.A., Model No. E10-10) were housed in sound-attenuating ventilated chambers located in a room saturated with masking white noise. Each chamber contained two levers, only one of which was operative during the experiment. The operative lever (left or right) was allocated randomly to the 8 subjects. Reinforcement consisted of standard 45 mg food pellets (Campden Instruments Ltd., U.K.). During the presentation of each food pellet a light came on for 160 msec in the food chamber, providing secondary reinforcement. A house light located in the roof of the chamber was continuously activated during operant sessions. Presentations of food and light stimuli were controlled by a Nova 3 computer (programmed in ACT-N language) located in an adjoining room. The computer was also used to record various features of the behaviour of each subject (see the Results section).

Procedure

Rats were initially trained (Mondays–Fridays) to respond for food reward. Food pellets were presented on a Random Time Schedule (Mean = 60 sec, range = 12–70 sec), and subjects were simultaneously rewarded on a fixed ratio one schedule. Once subjects had begun to respond, a fixed interval (FI) schedule was introduced and the interval duration increased progressively from 4–120 sec. The final schedule was therefore Fixed Interval 2 min. Operant sessions were always 60 min in duration. The first response in each session always led to food reward, subsequent responses were then rewarded on the FI 2 min schedule. After extensive baseline training (over 40 hours per subject), drug administration and control sessions were introduced. These were always conducted on Fridays, after animals had been maintained on the basic schedule from Mondays through Thursdays. Prior to the Friday sessions subjects received the relevant drug and control injections. On some control sessions no injections were given (see below).

The initial phase of the study was concerned with obtaining dose/effect curves for d-amphetamine and dl-cathinone on FI 2 min schedule maintained responding. These

dose/effect curves were obtained in the presence and absence of the 5HT receptor antagonist methysergide. Subjects therefore received two injections prior to each operant session. The first injection was either methysergide (dissolved in distilled water) or distilled water alone. The second injection was either d-amphetamine (dissolved in saline) or cathinone (in saline) or saline alone. (For drug doses see the Results section.) The first injection was given 15 min prior to the start of the session and the second injection 5 min prior to the session. Drug doses were administered in a nonsystematic random order. Data obtained on Mondays–Thursdays were used as baseline data to evaluate the effects of treatments given on the relevant Fridays.

As well as the drug treatments detailed above, three different types of control sessions were run. In a "Baseline Control" test, subjects were simply run on a Friday in the absence of any injections. The data obtained in this test (expressed as a percentage of data obtained on the previous Monday–Thursday) were used to assess stability of baseline behaviour. An "Injection Control" test involved subjects receiving the relevant solvents (distilled water and saline) 15 and 5 min respectively prior to a Friday operant session. A final control session, the "Methysergide Control," involved giving subjects Methysergide in distilled water 15 min prior to an operant session followed by saline 5 min prior to the session.

In the second phase of the experiment, time/effect curves were obtained for both cathinone and d-amphetamine. Drugs were injected on Fridays, either 30, 60, 120 or 180 min before each operant session. Cathinone and d-amphetamine (in saline) were administered at doses (5.0 mg/kg and 2.0 mg/kg respectively) that had been found, in the first phase of the study, to have approximately equieffective actions on FI operant responding when injected 5 min prior to the session. In this second phase of the experiment only *one* injection ever preceded operant sessions. Two control sessions were included in this phase of the study. A "Baseline Control," consisted, as in the first phase of the study, of an assessment of baseline response stability. Subjects were simply run in an operant session on a Friday, in the absence of any injections, and the data obtained were expressed as a percentage of the previous week's average response rate for each animal. An "Injection Control" consisted of running animals in a Friday session after a single injection of saline 30 min prior to the relevant session.

The whole experiment, involving both phases of the study, was run over a period of 10 months.

Drugs

d-Amphetamine sulphate (Smith, Kline and French, U.K.) and dl-cathinone oxalate (Dr. Hsj. X. Schorno, Cantonal Hospital, 6004 Lucerne, Switzerland) were dissolved in 0.9% sterile isotonic saline (Injection volume=2ml/kg). Methysergide dihydrogen maleate (Sandoz Products, U.K.) was dissolved in a large volume of distilled water (Injection volume=5 ml/kg) due to its low solubility and its instability in the presence of free chloride ions (Sandoz Products Information Sheet). Doses of d-amphetamine and cathinone were based on previous reports of the behavioural effects of these drugs. The 10 mg/kg dose of methysergide was selected on the basis of previous studies from this laboratory indicating that this dose of methysergide does not itself affect operant responding, but it does potentiate the actions of beta-phenylethylamine—the basic structural skeleton for both amphetamine and cathinone [18]. The timings of the injections of methysergide and cathinone/amphetamine were also based on these previous studies [18]. All drugs were injected intraperitoneally. All drug doses refer to the salts specified above.

TABLE 1

BASELINE RESPONSE RATE DATA

Subject	Response Level (Responses/Second)
1	0.3980 ± 0.013
2	0.3774 ± 0.019
3	0.6365 ± 0.020
4	0.6667 ± 0.013
5	0.9003 ± 0.029
6	0.6223 ± 0.025
7	0.6670 ± 0.015
8	0.4264 ± 0.016

Average baseline response rate data for each subject. Data are shown as mean (±S.E.) response rates/second averaged over 19 baseline values for each subject. Baseline values for each subject were the mean response rates for the Monday-Thursday of each of 19 weeks.

Statistics

Data were analysed by repeated measures ANOVAs and matched *t*-tests. Log dose/response curves were analysed with least squares linear regression techniques. Rate-dependency plots (in log-log coordinates) were calculated in two different ways (see the Results section) using least-squares linear regression techniques. All statistical tests were two-tailed.

RESULTS

Phase One of Study: Dose-Effect and Rate-Dependency Data

Table 1 shows the mean baseline response rate data for each subject calculated throughout phase one of the experiment. It is clear that subjects differed markedly in baseline response rates (from 0.377 to 0.900 response/sec). However, these baseline response rate differences were consistent over the whole experiment, as shown by the small standard errors for each individual subject.

Figure 1 shows log-linear dose/response curves for cathinone and d-amphetamine in the presence and absence of methysergide. The data are expressed as percentage response levels (see figure legend). Methysergide alone did not affect response level relative to the "Injection Control" (matched $t(7)=0.05$) or the "Baseline Control" (matched $t(7)=1.18$), which did not differ significantly from each other, matched $t(7)=2.17$, $p>0.05$.

The effects of cathinone and d-amphetamine were analysed by two separate 2 factor (Drug dose, presence or absence of Methysergide) ANOVAs, with repeated measures over both factors. For d-amphetamine, there was a highly significant effect of drug dose, $F(3,21)=26.5$, $p<0.001$, the effect of methysergide pretreatment approached, but did not actually reach, conventional levels of statistical significance ($F(1,7)=4.7$, $p<0.1$; critical value at $\alpha=0.05=5.59$).

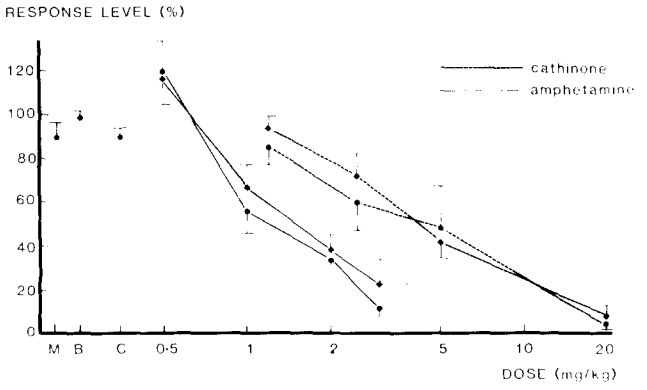

FIG. 1. Effects of cathinone and amphetamine on percentage response level on a FI 2 min schedule. Log dose/response curves for both drugs were obtained in the presence (circles) and absence (diamonds) of methysergide. Data are expressed as mean (±S.E.) percentage response levels. Response rates for each rat on drug sessions (Fridays) were calculated as a percentage of individual response rates on previous Monday–Thursday baseline days. Data plotted at M are for the "Methysergide Control." Data plotted at B are the "Baseline Control." Data plotted at C are for the "Injection Control."

For cathinone, there was a highly significant effect of drug dose, $F(3,21)=35.1$, $p<0.001$. There was no significant effect of methysergide pretreatment ($F<1$).

The predominant effects of cathinone and d-amphetamine were to suppress operant responding. However at the lowest dose of d-amphetamine tested (0.5 mg/kg) there was a significant tendency for d-amphetamine to increase response level relative to the "Injection Control," matched $t(7)=2.56$, $p<0.05$. For cathinone, there was no such tendency for response level to be elevated above the "Injection Control" level at the lowest dose (1.25 mg/kg) studied (matched $t(7)=0.68$).

Figure 1 shows that the log dose/response curves for cathinone were somewhat shallower than those for d-amphetamine. ED_{50} values for both drugs in the presence and absence of methysergide were calculated by least-squares linear regression analyses for each of the four dose/effect curves shown in Fig. 1. The ED_{50} was arbitrarily defined as that drug dose which suppressed response level to the 50% level. Chi^2 analyses indicated that all four calculated regression lines provided an accurate fit of the observed data points (since all four calculated values of Chi^2 gave p at least >0.10). The ED_{50} values (mg/kg) for cathinone and amphetamine were 4.72 and 1.62 in the absence of methysergide and 4.08 and 1.43 in the presence of methysergide. Thus the potency ratios for the two drugs were 1:2.9 in the absence of methysergide and 1:2.8 in its presence. dl-Cathinone can clearly be described as less potent than d-amphetamine in suppressing FI operant responding by a factor of approximately 1:3.

One of the most extensively investigated actions of d-amphetamine on operant behaviour is its tendency to increase low rates of responding and decrease high rates of responding, inducing a so-called rate-dependent drug effect. The only study that has to date investigated possible rate-dependent effects of cathinone produced relatively weak evidence for cathinone-induced rate-dependency [22]. We therefore analysed the data obtained in the present study to determine whether or not reliable evidence for rate-dependent effects of cathinone (and amphetamine) could be obtained. The conventional method of Dews [7] was used to assess rate-dependency. Local response rates for 12 sec units (deciles) of each 2 minute Fixed Interval were calculated for each subject, averaged over the whole of the one hour session. In these analyses, control response rates were derived from data obtained on the single day immediately preceding each drug day.

Figures 2 and 3 show conventional rate-dependency plots for Rats 1 and 2 under all doses of d-amphetamine and cathinone. For both animals, under both drugs, clear rate-dependent effects were observed. As previously reported

TABLE 2

SLOPES, Y-VALUES (I.E., RESPONSE RATES AFTER DRUG TREATMENT WHEN THE CONTROL RESPONSE RATE WAS 1 RESPONSE/SECOND), AND CORRELATION COEFFICIENTS (r) OF THE CALCULATED REGRESSION LINES

	Condition	Dose (mg/kg)	Slope	Y-Value (%)	r
Rat 1	d-Amphetamine	0.5	−0.386	106.0	−0.941
	d-Amphetamine	1.0	−0.764	45.7	−0.991
	d-Amphetamine	2.0	−0.839	28.3	−0.995
	d-Amphetamine	3.0	−0.875	21.6	−0.999
	dl-Cathinone	1.25	−0.177	89.8	−0.840
	dl-Cathinone	2.5	−0.705	62.1	−0.978
	dl-Cathinone	5.0	−0.898	25.7	−0.997
	dl-Cathinone	20.0	−0.999	16.3	−0.998
Rat 2	d-Amphetamine	0.5	−0.457	57.8	−0.980
	d-Amphetamine	1.0	−1.003	14.0	−0.995
	d-Amphetamine	2.0	−1.058	10.7	−0.977
	d-Amphetamine	3.0	−1.043	9.5	−0.945
	dl-Cathinone	1.25	−0.151	102.6	−0.662
	dl-Cathinone	2.5	−0.685	75.0	−0.989
	dl-Cathinone	5.0	−0.721	42.6	−0.992
	dl-Cathinone	20.0	−0.990	15.4	−0.994
Rat 3	d-Amphetamine	0.5	−0.247	128.3	−0.924
	d-Amphetamine	1.0	−0.266	54.3	−0.510
	d-Amphetamine	2.0	−0.821	43.9	−0.996
	d-Amphetamine	3.0	−0.960	8.6	−0.995
	dl-Cathinone	1.25	−0.169	92.9	−0.718
	dl-Cathinone	2.5	−0.664	37.0	−0.990
	dl-Cathinone	5.0	−0.758	56.7	−0.904
	dl-Cathinone	20.0	No data—responding totally suppressed by drug		
Rat 4	d-Amphetamine	0.5	−0.237	79.7	−0.885
	d-Amphetamine	1.0	−0.555	25.7	−0.775
	d-Amphetamine	2.0	−0.905	10.2	−0.997
	d-Amphetamine	3.0	No data—responding totally suppressed by drug		
	dl-Cathinone	1.25	−0.331	70.4	−0.674
	dl-Cathinone	2.5	−0.806	43.4	−0.999
	dl-Cathinone	5.0	−0.957	13.2	−0.998
	dl-Cathinone	20.0	−1.106	6.7	−0.981

The regression lines for Rats 1 and 2 are plotted in Figs. 2 and 3.

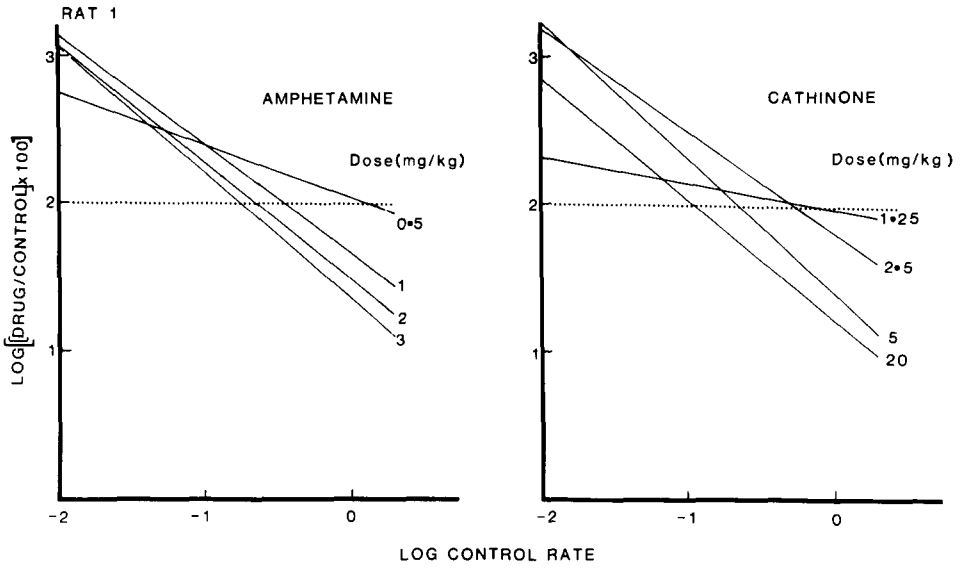

FIG. 2. Rate-dependency plot for Rat 1 under all doses of amphetamine and all doses of cathinone studied. Dotted lines on each graph indicate a drug effect equivalent to 100% of the previous nondrugged session at all control rates of responding. Continuous lines are the calculated least-squares regression lines for each drug dose. In calculating the regression lines shown, fixed interval deciles (12 second units) were discarded if the control response rate for the relevant decile was below 0.01 responses/sec (log −2). The regression lines are not extrapolated beyond 2.0 responses/second (log 0.3) because local response rates higher than this were not observed. Raw data points are not plotted on the graph for the sake of clarity, however Table 3 shows the correlation coefficients for each of the plotted regression lines.

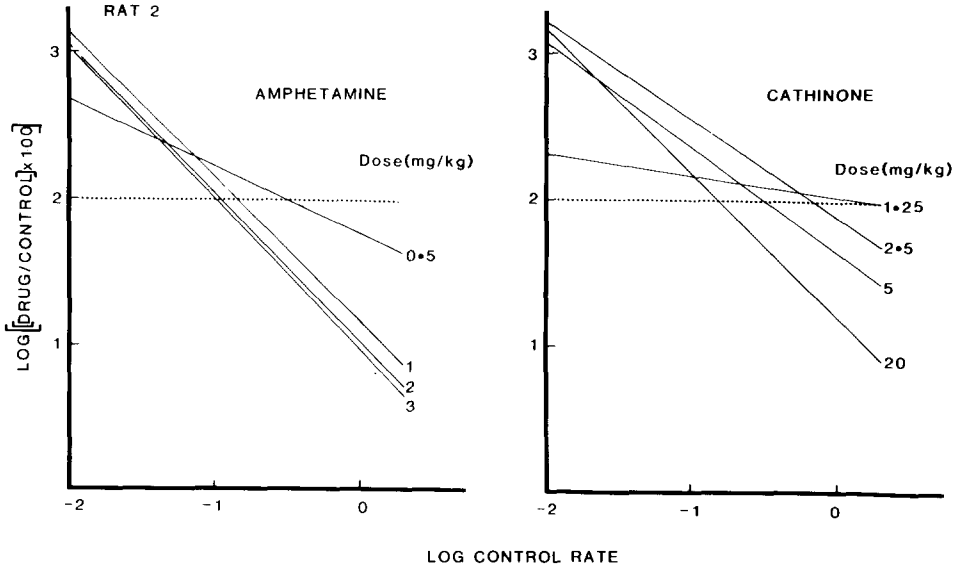

FIG. 3. Rate-dependency plot for Rat 2. For further details see legend to Fig. 2.

[39] such regression lines show increasing negative slopes with increasing drug dose. Table 2 shows data relevant to the calculation of the regression lines plotted in Figs. 2 and 3, and also includes data for two further animals (Rats 3 and 4) for whom the data have not been plotted graphically.

Table 2 indicates clearly that the regression lines plotted in Figs. 2 and 3 all have high correlation coefficients. For all subjects the slopes of the regression lines for both drugs became increasingly negative with increasing dose, tending towards −1.0 at the highest doses. The "Y-Value" data indicate that the response suppressant effects of both drugs were dose-related for each *individual* subject. Figures 2 and 3 and Table 2 demonstrate that when the rate-dependent effects of cathinone and d-amphetamine are evaluated in rats

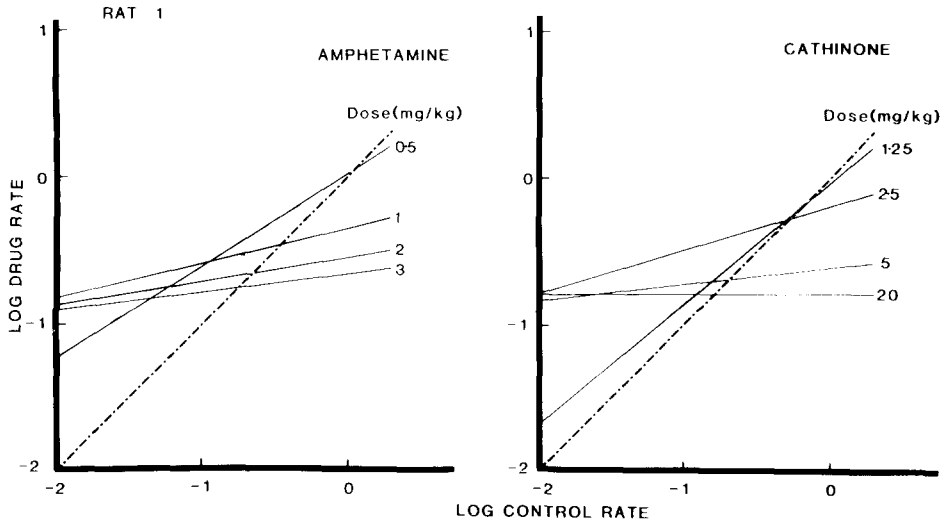

FIG. 4. Plot of absolute drugged rates of responding against absolute control rates of responding in log-log coordinates for Rat 1 (cf. Fig. 2). Calculated regression lines are shown for all of the doses of amphetamine and cathinone studied. The stippled line on each of the graphs shows a line of gradient equal to plus one, when drug rate is always equal to control rate. Least squares regression lines were calculated and plotted as described in the legend for Fig. 2. Raw data points are not plotted for the sake of clarity, however Table 4 shows the correlation coefficient for each of the plotted regression lines.

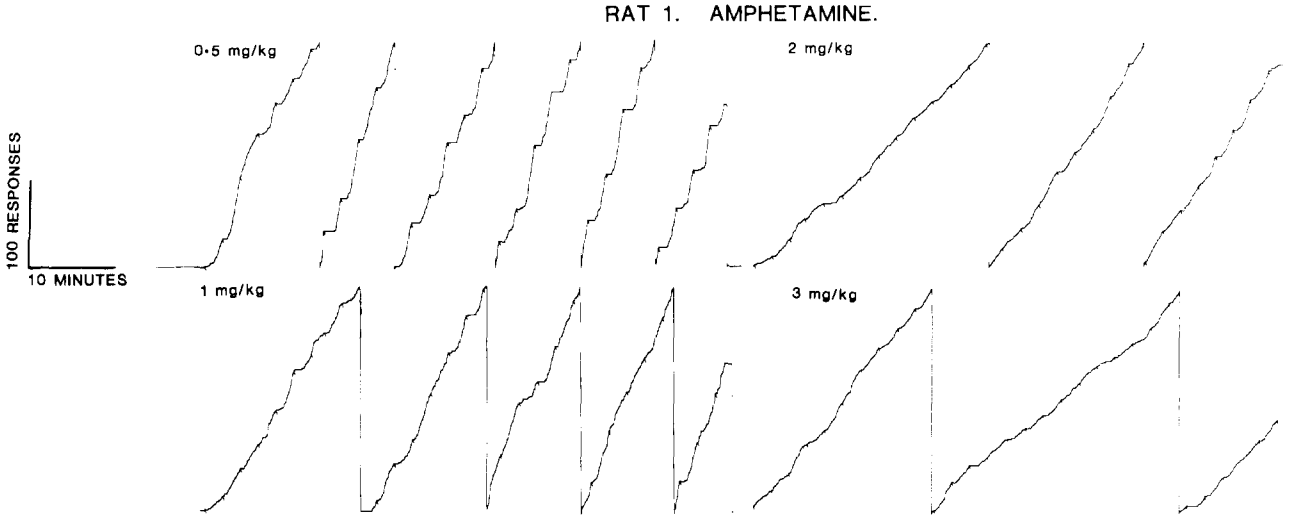

FIG. 5. Cumulative records for Rat 1 responding under 4 different doses of d-amphetamine. Each session under each dose of drug lasted for one hour, drugs being injected 5 min prior to each session. Sideways deflections on the record indicate presentations of rewards under the FI 2 min schedule. The pen reset after 260 responses.

with conventional rate-dependency plots [7], then the effects of cathinone closely resemble the rate-dependent effects of amphetamine. However, the method used above to plot rate-dependent drug effects is not without its critics [4, 16, 35]. Although such rate-dependency plots have been [7] and are still [31,40] widely used, these conventional plots have been criticised as being misleading about the true nature of drug effects because they express them in relative rather than absolute terms [4, 16, 39]. If a drug induces a *constant* rate of responding throughout the Fixed Interval conventional rate-dependency analysis [7] produces plots such as those shown in Figs. 2 and 3, in which the slope tends towards, but does not exceed −1.0 as drug dose increases [4, 35, 39]. A constant rate of responding throughout the Fixed Interval can clearly be considered to reflect a situation in which drug actions cannot be *dependent* on the control rate of responding. Thus, although graphs such as those shown in Figs. 2 and 3 are not in any sense mathematically invalid, they may be potentially misleading about the nature of drug effects when drugs induce rate constancy [35,39]. It has therefore been argued that rate-dependent drug effects should be plotted as log-log plots of absolute rates under drug against absolute control rates [4,16]. Since there is not universal agreement as to the relative merits of these

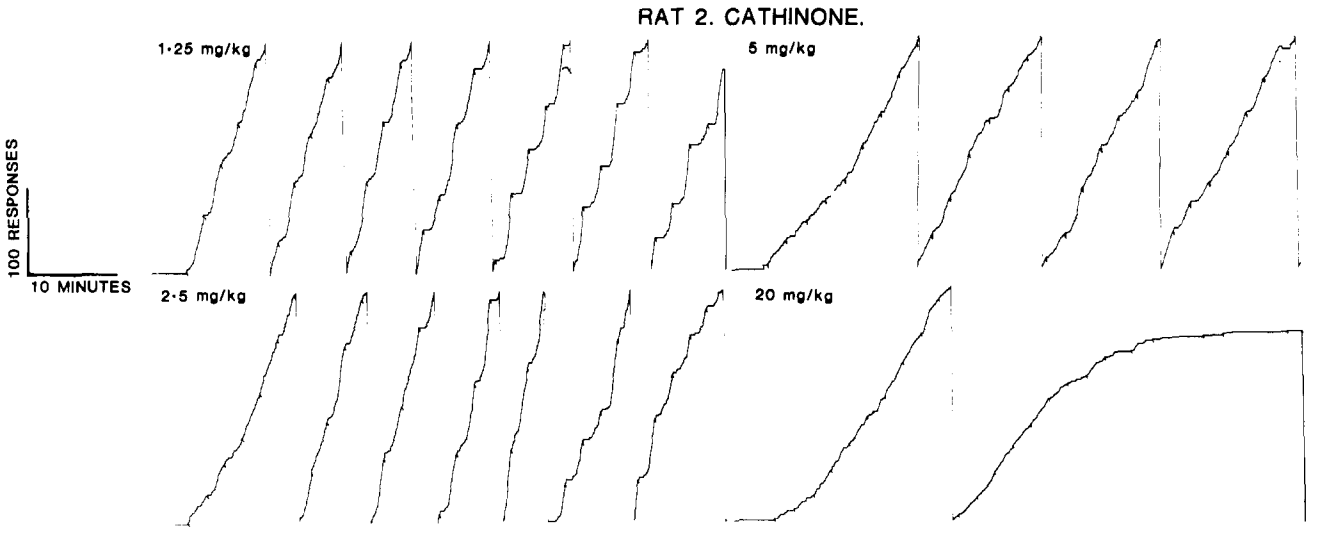

FIG. 6. Cumulative records for Rat 2 responding under 4 different doses of dl-cathinone. For other details see legend to Fig. 5.

TABLE 3

SLOPES, Y-VALUES (I.E., RESPONSE RATES PER SECOND AFTER DRUG TREATMENT WHEN THE CONTROL RESPONSE RATE WAS 1 RESPONSE/SECOND) AND CORRELATION COEFFICIENTS (r) OF THE CALCULATED REGRESSION LINES

Rat 1	Condition	Dose (mg/kg)	Slope	Y-Value	r
	d-Amphetamine	0.5	0.614	1.063	+0.978
	d-Amphetamine	1.0	0.237	0.457	+0.916
	d-Amphetamine	2.0	0.161	0.283	+0.893
	d-Amphetamine	3.0	0.125	0.216	+0.956
	dl-Cathinone	1.25	0.823	0.898	+0.992
	dl-Cathinone	2.5	0.295	0.621	+0.890
	dl-Cathinone	5.0	0.103	0.249	+0.829
	dl-Cathinone	20.0	0.001	0.164	+0.002

methods of plotting rate-dependent drug effects [39], the most conservative approach is to plot data in both the conventional form [7] and in the more recently recommended [4,16] drug rate against control rate format. This conservative approach will indicate graphically whether or not rate-dependent drug effects shown with conventional plots are due (at least in part) to drug-induced rate constancy (cf. [44]). We have therefore analysed and plotted the data (see Fig. 4) from one of the subjects reported on above (Rat 1) in terms of the more recently recommended [4,16] drug rate against control rate procedure. Table 3 shows the slopes, Y-values (at 1.0 response/second) and the correlation coefficients for each of the plotted regression lines.

For both d-amphetamine and cathinone there was a progressive tendency towards rate-constancy as drug dose was increased. All the regression lines (except that for cathinone at 20 mg/kg. See Table 3) have high correlation coefficients. As expected [39] the slopes of the regression lines indicate that the effect of plotting the data in the format shown in Fig. 4 is to rotate the slope of each regression line by a factor of plus one relative to the slopes plotted in Fig. 2. Thus, the two forms of plotting the data are obviously mathematically related [4,39]. However, the rate-dependency effects shown in Figs. 2 and 3 can clearly be attributed, at least in part, to a progressive tendency towards rate-constancy with increasing drug dose. This conclusion is supported by examination of cumulative records for subjects responding under both drugs (Figs. 5 and 6). These show quite clearly that, as drug dose increased, subjects' response rates showed rate constancy at higher drug doses.

Phase Two of Study: (Time/Effect Data)

Figure 7 shows the time/effect data obtained for cathinone and amphetamine injected at various times before operant sessions.

These data were analysed by a two factor (time after injection, type of drug treatment) ANOVA, with repeated measures on both factors. There was a highly significant effect of time after injection, $F(3,21)=15.56$, $p<0.001$, no effect of type of drug treatment ($F(1,7)<1$) and no significant drug × time interaction ($F(3,21)<1$). Comparison of response level data observed at 180 min post injection with both sets of control data indicated that at this time amphetamine treated subjects did not differ significantly from the baseline (B) level (matched $t(7)=0.67$), or from the injection control (C) level (matched $t(7)=0.24$). Similarly, at this time, cathinone treated subjects did not differ significantly from either the baseline (B) level (matched $t(7)=0.88$) or the injection control (C) level (matched $t(7)=0.37$). In contrast, at 30 min post injection, cathinone significantly suppressed responding relative to both the baseline (B) level, matched $t(7)=4.50$, $p<0.01$, and the injection control (C) level, matched $t(7)=4.68$, $p<0.01$. Similarly, amphetamine at 30 min significantly suppressed responding relative to both the baseline (B) control level, matched $t(7)=5.29$, $p<0.01$, and the injection (C) control level, matched $t(7)=3.38$, $p<0.02$. The baseline control level (B) did not differ significantly from the injection control (C) data (matched $t(7)=1.06$).

These data indicate unequivocally that equipotent doses of dl-cathinone and d-amphetamine had identical durations of action in suppressing operant responding. The effects of

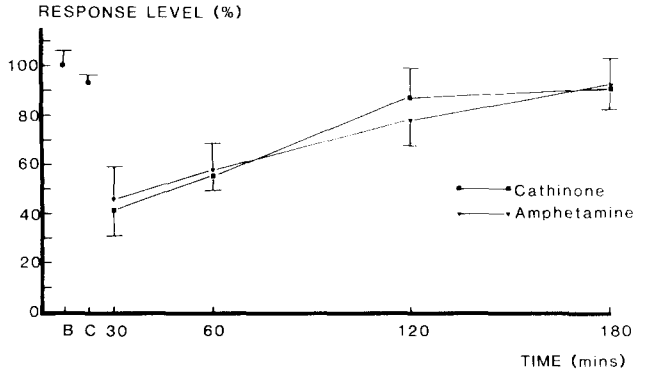

FIG. 7. Time/effect curves for d-amphetamine and dl-cathinone injected at different times before operant sessions of 1 hour's duration. Data are expressed as mean (±S.E.) percentage response levels. Data plotted at B are the "Baseline Control" data, the data plotted at C are "Injection Control" data. Amphetamine was always injected at 2.0 mg/kg, cathinone at 5.0 mg/kg. These doses were approximately equipotent in suppressing operant responding in the first phase of the study (see Fig. 1).

2.0 mg/kg of d-amphetamine and 5.0 mg/kg of cathinone were completely abolished by a 3 hour injection to operant session interval (Fig. 7).

DISCUSSION

The results of the first phase of the study indicated that the effects of both cathinone and d-amphetamine on overall rates of operant responding on the FI schedule were predominantly suppressant, although at the lowest dose studied (0.5 mg/kg) d-amphetamine produced a small elevation in overall response level (Fig. 1). The failure of d-amphetamine to produce marked rate-increasing effects on overall response rates with subjects on FI operant schedules is probably due to the fact that such effects are typically only seen with FI schedules if the Fixed Interval is of a relatively long duration, i.e., greater than the FI 2 min schedule used in this study [31]. The fact that cathinone's effects on the overall level of operant responding were predominantly rate suppressant is in accord with the findings of Johanson and Schuster [22] although it is possible that doses of cathinone lower than those studied here *might* actually have elevated overall rates of responding. In this specific study the effects of cathinone and d-amphetamine on overall rates of responding were very similar, with the caveat that cathinone appeared to produce a somewhat shallower dose/effect curve than d-amphetamine. Since the effects of psychostimulant drugs on operant behaviour may be explained in terms of drug-induced behavioural disruption and response competition [39], it is possible that the shallower dose/effect curve observed with cathinone indicates that cathinone and d-amphetamine have subtle differences in their motoric effects (cf. [9]). This hypothesis is clearly tentative in the absence of more definitive data. Foltin (Personal Communication, 1984) has indicated that in tests of drug-induced anorexia the dose/response curve for d-amphetamine is significantly steeper than that for l-cathinone (see data reported in [11]), in accord with the findings reported here. Detailed analyses of the motoric effects of these two stimulants might illustrate qualitative differences between them since drug effects on motor output are believed to mediate, at least to some extent, stimulant drug actions on *both* food intake and operant responding [39].

In this study pretreatment with methysergide did not cause statistically significant differential effects on the behavioural actions of d-amphetamine and cathinone. Recent evidence [5] indicates that, at the relatively high dose of methysergide studied here (10 mg/kg), this drug may have mixed agonist/antagonist actions on 5HT receptors in the rat. Such actions could clearly complicate attempts to demonstrate differential effects of manipulations of 5HT systems on the behavioural actions of cathinone and d-amphetamine.

The relative potency of dl-cathinone to d-amphetamine in suppressing FI operant responding in this study was approximately 1:3. It is, however, important to note that, in this study (and in our related studies) the potency ratio of dl-cathinone relative to d-amphetamine was calculated on the basis of weight rather than on a molar basis. Furthermore, it should be stressed that in these studies dl-cathinone was utilised. This compound consists, by definition, of a combination of the d- and l-isomers of the drug, the l-isomer generally being considered to be more active than the d-isomer (e.g., [15]). Thus the 1:3 potency ratio reported here must be qualified in that it can only be compared *directly* with other procedures which have calculated potency ratios by weight in studies comparing dl-cathinone to d-amphetamine. The calculated potency ratio of 1:3 for suppression of operant responding is in reasonably good agreement with other data reported in a variety of behavioural tests which have compared *racemic* cathinone with d-amphetamine. Thus, in other behavioural studies conducted in this laboratory we have reported that the potency ratio (by weight) of d-amphetamine to dl-cathinone in the drug discrimination procedure is 1:2, and it is 1:3 in tests of drug-induced adipsia [19]. In tests of drug-induced anorexia a potency ratio of 1:2 (by weight) was reported for dl-cathinone and d-amphetamine [9]. Zelger *et al.* [54] published data which indicate that the potency ratio of dl-cathinone to d-amphetamine can be estimated (by the present author) at 1:4 in inducing locomotor stimulation in mice ([54], Fig. 2) and at 1:3 in inducing stereotypy in rats ([54], Fig. 4). Similarly, Johanson and Schuster [22] reported that in monkeys the potency ratio of these drugs in inducing suppression of behaviour maintained by a multiple FI/FR schedule was between 1:2 and 1:4. Furthermore, the potency ratio of these forms of the two drugs in inducing lethality was reported to be 1:3 [21]. It is clear that the pharmacological effects of dl-cathinone are generally less potent than those of d-amphetamine by a factor of between 1:2 and 1:4. A notable exception to this rule is the finding in our laboratories [19] that the potency ratio (by weight) of d-amphetamine to dl-cathinone in inducing conditioned taste aversion (C.T.A.) is unexpectedly high, being 1:17. These data support a previous suggestion [8] that the action of cathinone in the C.T.A. procedure is remarkably weak. The low potency of cathinone in the C.T.A. procedure might plausibly be attributed to pharmacokinetic factors, since the actions of drugs in the C.T.A. procedure *may* be determined by their durations of actions [17]. However, the systematic comparison reported above (Fig. 7) of the durations of action of cathinone and d-amphetamine is clearly *not* in accord with this analysis, since the drugs had similar durations of actions. Furthermore, in other behavioural studies cathinone and amphetamine have been found to have equivalent durations of action [14, 19, 52, 53, 54]. Thus Johanson and Schuster's [22] suggestion that cathinone might be shorter acting

than amphetamine is probably incorrect. It therefore seems unlikely that cathinone's low potency in the C.T.A. procedure can be attributed simply to factors related to its duration of action. The low potency of cathinone in the C.T.A. procedure, *is* however, of considerable interest in the light of recent evidence [50] that cathinone is a very potent reinforcer in the operant self-administration procedure. Cathinone appears to share a profile of actions with cocaine in that both drugs are highly potent reinforcers and very weak agents in inducing C.T.A. In the latter respect they differ from amphetamine which is a potent C.T.A.-inducing agent. It is possible that the actions of drugs in the C.T.A. and self-administration procedures are related and that although cathinone resembles amphetamine structurally, its overall pharmacological profile may ultimately prove to be more similar to that of cocaine, suggesting that it may well have a higher abuse potential than amphetamine due to its weaker aversive properties. Clearly this hypothesis can only be validated by further research.

The data reported here provide clear evidence that the actions of cathinone (and amphetamine) can be considered rate-dependent when the data are plotted in the form of conventional [7] rate-dependency plots (see Figs. 2 and 3). Thus we have provided more reliable evidence for rate-dependent effects of cathinone than a previous study in rhesus monkeys [22].

In the rate-dependency analyses reported above the slopes of the regression lines relating the drug effects to the control rates of responding (in a log/log plot) tended progressively towards minus one with increasing drug dose without ever substantially exceeding minus one (see Figs. 2 and 3 and Table 2). As noted by Gonzalez and Byrd [16] and others [35], such data can be interpreted as implying that there is a progressive increase with drug dose towards rate constancy (cf. [4]) or rate convergence [35] when the drug induces a constant rate of responding *regardless* of the baseline rate of responding. This interpretation of the data reported here with cathinone (and amphetamine) is supported by plotting the data in the format recommended by Gonzalez and Byrd [16] in which absolute rates of responding under drug are plotted against control rates in log/log coordinates (see Fig. 4). This form of rate-dependency analysis makes it abundantly clear that the rate-dependent effects of cathinone observed in conventional [7] rate-dependency plots (Figs. 2 and 3) are actually due, in large part, to drug-induced rate constancy [4] or rate convergence [35]. This interpretation of the data reported above is clearly supported by examination of the cumulative records generated by drugged animals (Figs. 5 and 6) which show a progressive tendency with drug dose towards rate constancy over the whole of the operant session. It should, however, be stressed that it *is* possible to obtain conventional rate-dependency effects [7] with drugs that do *not* produce rate constancy [44], so that the value of calculating both types of rate-dependency plots would seem considerable in order to determine whether rate-dependent drug effects obtained with conventional plots [7] are, or are not, due to drug-induced rate constancy or rate convergence. To have merely analysed the data obtained with cathinone (and amphetamine) in the conventional form would have obscured the rate constancy induced by these drugs (cf. [22]).

However, whilst it is obvious from the data reported above that the actions of cathinone, like those of amphetamine, can be described as rate-dependent, or perhaps more accurately, as rate-convergent [35], it is not clear from the data reported here why both drugs have such effects. A number of different explanations of such effects have been put forward [39]. Firstly, it is possible that the apparent rate-dependent effects of cathinone and amphetamine may be due to drug-induced disruption of stimulus control of the differential rates of responding typically generated throughout the Fixed Interval so that subjects no longer detect the stimuli controlling differential responding. Such an effect might be due [35,37] to the fact that both drugs have potent discriminative stimulus properties themselves [6, 19, 42] which disrupt stimulus control by acting as a novel stimulus and produce a constant rate of responding through a schedule of reinforcement (see [37] for a full discussion of this hypothesis). Alternatively, it has been argued that the rate-dependent effects of amphetamine-like drugs may result from drug-induced motor stimulation with simultaneous facilitation of response competition (see [39]). The data reported here do not allow a distinction to be drawn between these alternative mechanistic accounts of rate-dependency, it is even possible that *both* mechanisms are implicated in the reported effects. However, regardless of the mechanism(s) involved in the rate-dependent effects of cathinone and amphetamine reported here, the overall pattern of the data indicates unequivocally that both drugs have very similar gross effects over similar time courses on Fixed Interval responding. Thus the data reported here highlight further the similarities between the behavioural effects of cathinone and other psychostimulant drugs (although subtle differences between the behavioural actions of cathinone and amphetamine *may* exist). Cathinone therefore appears to be an important, relatively novel, psychostimulant drug whose actions merit further analysis. In particular, the potent reinforcing effects of cathinone [50] coupled with its surprisingly weak aversive properties [8,19] suggest that this compound may be of considerable value in analysing the behavioural and neurochemical substrates of drug abuse.

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