

COMPARATIVE POTENCIES OF AMPHETAMINE, FENFLURAMINE AND RELATED COMPOUNDS IN TASTE AVERSION EXPERIMENTS IN RATS

D.A. BOOTH & C.W.T. PILCHER¹

Department of Psychology, University of Birmingham

G.D. D'MELLO & I.P. STOLERMAN

MRC Neuropharmacology Unit, The Medical School, Birmingham B15 2TJ

- 1 Rats failed to drink a flavoured solution when its consumption had been followed by injection of amphetamine (conditioned taste aversion).
- 2 There was very little difference between the potencies of (+)- and (–)-amphetamine.
- 3 *p*-Chloromethamphetamine was a more potent aversive agent than methamphetamine.
- 4 Strong taste aversions were also conditioned with other congeners of amphetamine. The rank order of potency was: fenfluramine > chlorphentermine > *p*-hydroxyamphetamine.
- 5 Cocaine induced only moderate taste aversions, even at high doses.
- 6 Aversive potency did not appear to be correlated with known neurochemical actions of the drugs or with behavioural stimulation, but appeared to be a central action which may have been linked to anorexigenic potency or time course of action.

Introduction

It has been established that rats can learn to reject distinctively flavoured solutions if their consumption is followed by administration of large doses of lithium or apomorphine (Garcia & Ervin, 1968; Revusky & Garcia, 1970). Such rats are said to exhibit 'conditioned taste aversions' (CTA); many hypotheses have been presented as to what actions of the drugs produce CTA, but no mechanism has been generally agreed. More recently, it has become apparent that many different psychoactive drugs can elicit CTA and that it is not always necessary to use large doses (Cappell & Le Blanc, 1975). For example, amphetamine is active in doses ranging upwards from 0.1 mg/kg (Cappell & Le Blanc, 1973; Booth, D'Mello, Pilcher & Stolerman, 1976). Studies with congeners of amphetamine have also been reported (Martin & Ellinwood, 1974; Goudie & Thornton, 1975; Goudie, Thornton & Wheeler, 1976). However, comparisons between different drugs can be misleading unless a range of doses of each substance is studied with a standardized experimental procedure; with occasional exceptions (e.g. Carey & Goodall, 1974), this has not been attempted.

The aim of the present experiments was to determine the relative potencies of (+)-amphetamine and some related compounds. These included (–)-amphetamine, *p*-hydroxyamphetamine, cocaine and some halogen-substituted derivatives of amphetamine (e.g. fenfluramine). It was known from earlier work that there were differences between the profiles of action of these substances, and it was hoped that effects such as anorexia, or actions on particular neurochemical systems, could be correlated with potency in the flavour aversion procedure.

Methods

Animals

Male, hooded rats bred in the Department of Psychology, University of Birmingham were used throughout. The overall range of weights was 180–300 g, but in any one experiment the range was smaller. The rats were housed individually in a room maintained at about 22°C, and a regular light-dark cycle was imposed by fluorescent lighting (light from 08 h 00 min–20 h 00 min).

¹ Present address: Department of Pharmacology, University of Kuwait. P.O. Box 5969, Kuwait.

Ten days after the rats arrived in the laboratory, their access to water was restricted to 1 h per day (10 h 00 min–11 h 00 min). All rats remained on this regimen for 10 days before any flavoured solutions were presented, and on all days between flavour presentations throughout the rest of the experiment. All fluids were presented in calibrated glass tubes.

Conditioning procedure

The procedure was similar to that used by Booth *et al.* (1976), and involved the development of discrimination between two different flavours, one paired with drug injections and the other with 0.9% w/v NaCl solution (saline). After the 10-day period of adaptation to the regimen of water presentation, one of these flavours was presented for 15 min on every second day (beginning at 10 h 00 min). The two flavours were presented alternately, and thus each flavour was presented to a given rat on every fourth day. Immediately after the flavoured solutions were removed, the rats were injected with either a drug or saline (flavour-injection 'pairing'). For half of the rats in which a given drug dose was being tested, one flavour was repeatedly paired with that dose, whereas the other flavour was repeatedly paired with saline. The flavour-injection pairings were reversed in the remaining rats, thus ensuring that effects of the unconditioned palatabilities of the flavours were balanced out in the averaged results. The order of drug and saline injection was also counterbalanced at each drug dose. Distilled water was presented from 16 h 30 min–17 h 15 min, so that the rats continued to have access to fluid for a total of 1 h each day.

After four flavour-drug and four flavour-saline pairings ('single-stimulus tests'), injections were stopped. Two days later, drug and saline-paired flavours were presented simultaneously for 15 min ('two-stimulus test'). On the next day, the positions of the two stimuli (flavours) were reversed to balance out side preferences. Only the mean scores for the two days of two-stimulus tests will be presented in the Results section.

Doses of drugs were selected on the basis of earlier work, and were normally spaced logarithmically in such a way that every alternate dose increased by a factor of 10 (e.g. 0.32, 1.0, 3.2, 10.0 mg/kg). A different group of rats was tested at each dose. Due to the large numbers of animals involved, it was not possible to test all drugs on the same batch of rats, but all drug data were compared with the saline scores derived from the same rats. When a comparison between a particular pair of drugs was of special interest, equal doses of the two substances were normally tested in the same batch of rats.

In the case of two drugs only, (+)- and (-)-amphetamine, a supplementary experiment was carried out with a procedure modified to permit further exploration of their relative potency. The

modification consisted of delaying all injections until 45 min after the flavoured solutions had been removed. Increasing the interval between flavour intake and drug administration can weaken conditioning (Garcia, Ervin & Koelling, 1966). This factor seemed especially relevant to the isomers of amphetamine because a difference in their time course of action (Segal, 1975) might have accounted for a discrepancy between our observations and those made by Carey & Goodall (1974).

Drugs

All drugs were dissolved in isotonic saline and were injected intraperitoneally in a volume of 1 ml/kg. Doses were expressed as salts, which were as follows: (+)-amphetamine sulphate (Smith, Kline & French or K. and K. Laboratories), (-)-amphetamine sulphate (Menley & James), (+)-methamphetamine hydrochloride (Sigma), (+)-*p*-chloromethamphetamine hydrochloride (Regis), fenfluramine hydrochloride (Servier), chlorphentermine hydrochloride (Lundbeck), cocaine hydrochloride (B.P.) and (+)-*p*-hydroxyamphetamine hydrobromide (Smith, Kline & French).

Solutions with synthetic 'chicken' and 'lemon' flavours were similar to those used by Lovett & Booth (1970) and by Booth *et al.* (1976) and were prepared in distilled water (all constituents from BDH Chemicals). Chicken flavour consisted of monosodium glutamate (12.5 mM) and sodium chloride (128 mM). Lemon flavour consisted of citric acid (1 mM) and sodium saccharin (2 mM).

Statistical analyses

The rates of change (linear regression coefficients) of flavour intake over the four single-stimulus tests were calculated separately for each rat for drug- and saline-paired flavours. Using these coefficients as indices of aversion, *t* tests or single-factor or two-factor analyses of variance were performed, using repeated measure methods where appropriate (Winer, 1971). Occasional, rapid development of extreme aversion after only one or two trials caused deviations from linearity, so that regression coefficients calculated as described above became misleading; therefore, when the mean intake on a given trial was less than 2 ml, results from subsequent trials were not included in the calculation of regression coefficients for that group.

For the two-stimulus tests, the amount consumed of the fluid having the flavour previously paired with drug was calculated as a percentage of the total fluid intake for each rat. These percentage scores were subjected to the arc-sine transformation to normalize their distributions (Winer, 1971), and then *t* tests or analyses of variance were carried out to determine whether the means differed significantly from 50%.

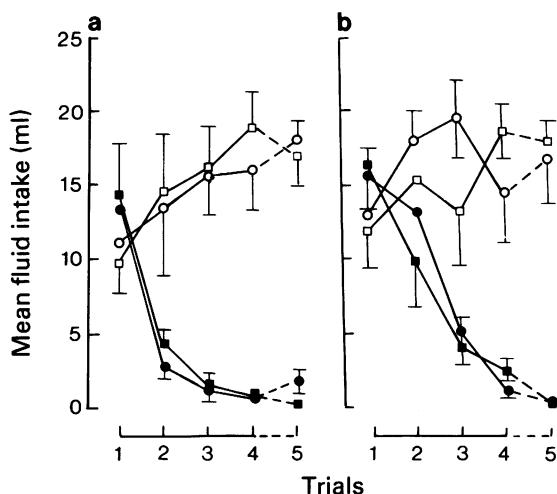


Figure 1 Flavour aversion conditioned with (+)-amphetamine (●, $n=4$) and (-)-amphetamine (■, $n=4$) at 3.2 mg/kg (a) and 1.0 mg/kg (b). In the same rats, intakes of saline-paired flavours were not suppressed (○ and □). Vertical bars in this and subsequent figures show one s.e. each side of the mean, with overlapping bars omitted for clarity.

Results

(+) and (-)-Amphetamine

The conditioning of flavour aversions at two doses of (+)- and (-)-amphetamine is shown in Figure 1. The mean intakes of amphetamine-paired flavours fell precipitously over their successive presentations, whereas the intakes of saline-paired flavours tended to increase. The overall differences between the aversion indices (single-stimulus tests) for amphetamine- and saline-paired flavours were highly significant with doses of 3.2 mg/kg ($F=70.8$, d.f. 1,6, $P<0.001$) and 1 mg/kg ($F=20.4$, d.f. 1,6, $P<0.01$). The development of discriminative taste aversions was confirmed in the two-stimulus tests, where both drug- and saline-paired flavours were presented simultaneously (Figure 1, trial 5). It can be seen that the CTA developed more rapidly with amphetamine administered at doses of 3.2 mg/kg (Figure 1a) than at doses of 1 mg/kg (Figure 1b), but at neither dose was there any significant difference between (+)- and (-)-amphetamine ($F<1$, d.f. 1,6 in both cases).

The results at lower doses are not presented in detail, but are included in Figure 2 which summarizes the data from all doses which were tested. The intakes of saline-paired flavours were not affected by the dose level of amphetamine which was paired with the alternate flavour; the results for saline-paired flavours

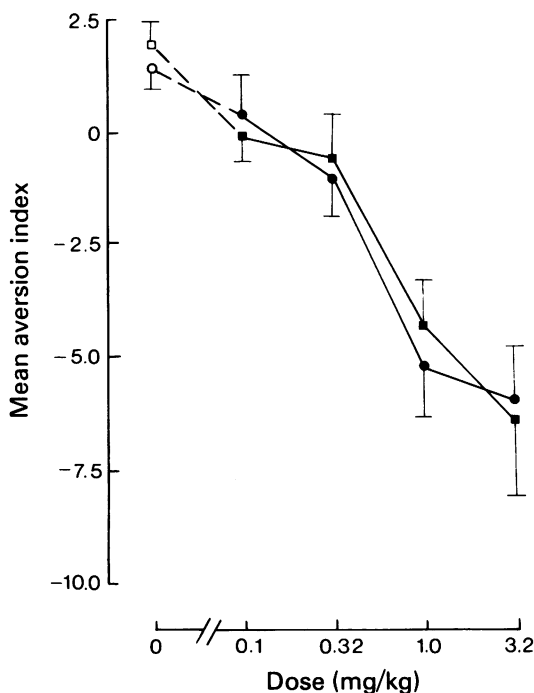


Figure 2 Dose-response curves for flavour aversions conditioned with (+)-amphetamine (●, $n=4$) and (-)-amphetamine (■, $n=4$). Abscissa scale, dose; ordinate scale, mean aversion index (ml/trial) from single-stimulus tests. Pooled results for saline-paired flavours provided control data for the same rats (○ and □).

have therefore been pooled to yield the baseline data (0 mg/kg) for Figure 2. Clear dose-response relations for aversions to amphetamine-paired flavours could be seen, and it was obvious that there was no substantial difference between the potencies of (+)- and (-)-amphetamine in this test.

Aversive dose (AD_{50}) was estimated by interpolation from the dose-response curves as that dose which would have been expected to produce an aversion index of -2.5 ml/trial, about half the aversion index produced by the highest doses of amphetamine which were tested. The AD_{50} values were 0.47 and 0.56 mg/kg for (+)- and (-)-amphetamine respectively. However, Carey & Goodall (1974) found that (+)-amphetamine was about four times as potent as (-)-amphetamine with a flavour aversion technique. A supplementary experiment was therefore carried out to compare the potency of the two isomers when greater delay intervened between flavour intake and injections, thus matching more closely the procedure used by Carey & Goodall. Figure 3a shows that this manipulation had no substantial influence on the

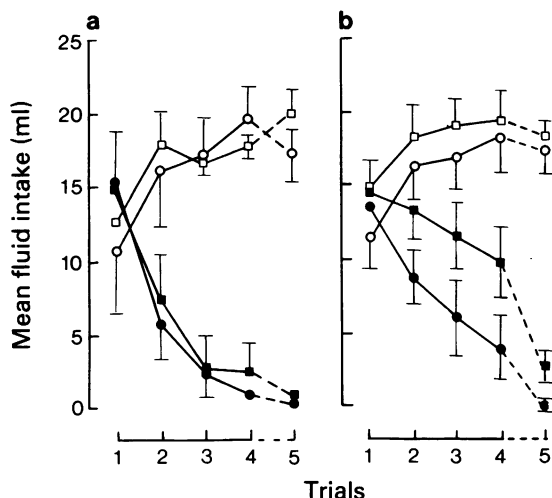


Figure 3 Flavours aversions conditioned with (+)-amphetamine (●) and (-)-amphetamine (■) at 3.2 mg/kg (a) and 1.0 mg/kg (b). In the same rats, intakes of saline-paired flavours were not suppressed (○ and □). In this experiment only, all injections were delayed until 45 min after flavoured solutions were removed. The degree of aversion produced by the two isomers of amphetamine did not differ appreciably at a dose of 3.2 mg/kg ($n=4$), but (+)-amphetamine produced greater aversion than (-)-amphetamine at a dose of 1 mg/kg ($n=8$).

effects of the two isomers at a dose of 3.2 mg/kg. However, at a dose of 1 mg/kg the mean aversion index for (+)-amphetamine was significantly greater than that for (-)-amphetamine ($F=6.93$, d.f. 1, 14, $P<0.05$). This difference was confirmed in the two-stimulus tests ($F=8.72$, d.f. 1, 14, $P<0.05$). This effect of delayed injection was not produced by low doses injected without delay (Figure 2).

Methamphetamine and p-chloromethamphetamine

The aversive activity of a halogen-substituted amphetamine, *p*-chloromethamphetamine, was investigated next, and compared with the equivalent unsubstituted methamphetamine at three dose levels. Figure 4a shows the results for flavours paired with methamphetamine at a dose of 1 mg/kg; significant CTA was obtained on both single-stimulus ($t=5.08$, d.f. 3, $P<0.05$) and two-stimulus tests ($t=17.6$, d.f. 3, $P<0.001$). Aversions with smaller doses of methamphetamine were much weaker, but were clearly apparent on the two-stimulus tests which are known to be more sensitive (Figure 4b, trial 5). Dose-related flavour aversions also developed when *p*-chloromethamphetamine was the conditioning agent (Figure 5). At a dose of 1 mg/kg, CTA was significant on both single-stimulus tests ($t=5.03$, d.f. 3, $P<0.05$) and two-stimulus tests ($t=12.2$, d.f. 3, $P<0.01$). The mean aversion index at a dose of 0.32 mg/kg was -3.1 ml/trial, and thus Figure 5b illustrates an intensity of aversion near to the criterion level (-2.5 ml/trial) selected for AD_{50} estimations.

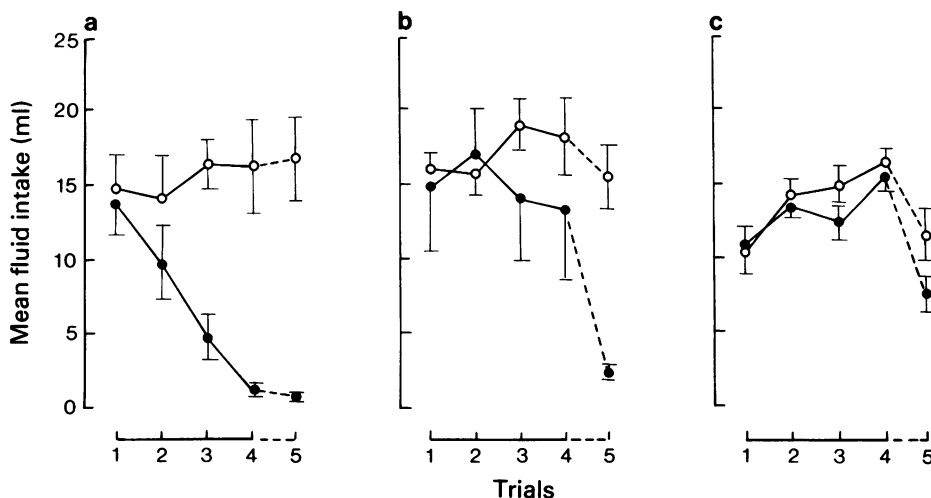


Figure 4 Flavour aversions conditioned with methamphetamine (●) in three groups of rats at 1.0 mg/kg (a), 0.32 mg/kg (b) or 0.10 mg/kg (c) ($n=4$); in the same rats, intakes of saline-paired flavours were not suppressed (○). Degree of aversion was clearly related to drug dose.

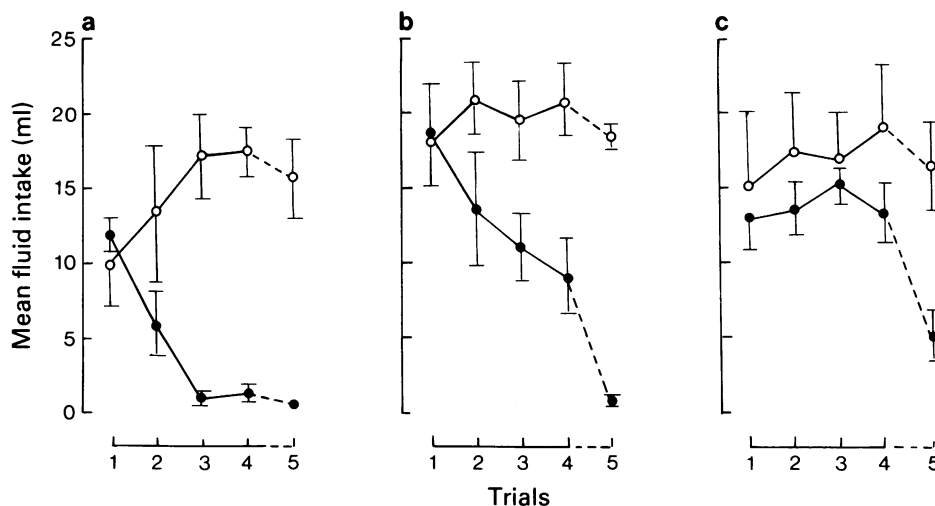


Figure 5 Flavour aversions conditioned with *p*-chloromethamphetamine (●) in three groups of rats at 1.0 mg/kg (a), 0.32 mg/kg (b) or 0.10 mg/kg (c) ($n=4$). In the same animals, intakes of saline-paired flavours were not suppressed (○). Degree of aversion was clearly related to drug dose.

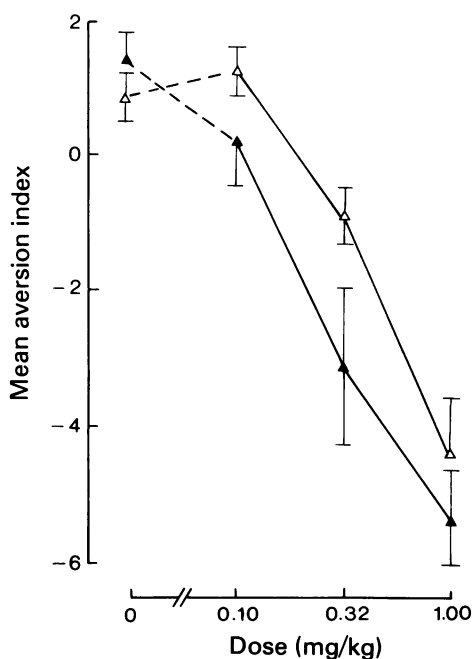


Figure 6 Dose-response curves for flavour aversions conditioned with methamphetamine (Δ) or *p*-chloromethamphetamine (\blacktriangle). Abscissa scale, drug dose; ordinate scale, mean aversion index (ml/trial) from single-stimulus tests. Four rats were tested at each dose and the intakes of saline-paired flavours in the same animals were pooled to provide control data (0 mg/kg).

Dose-response curves for the aversive effects of methamphetamine and *p*-chloromethamphetamine are shown in Figure 6. The overall difference in the degree of aversion as a function of dose was highly significant ($F=29.4$, d.f. 2, 18, $P<0.001$). *p*-Chloromethamphetamine also produced significantly greater aversion than methamphetamine ($F=5.59$, d.f. 1, 18, $P<0.05$). This difference between the potency of the two drugs was confirmed by analysis of the two-stimulus tests; again, there were significant differences due to dose level ($F=25.1$, d.f. 2, 18, $P<0.001$) and between drugs ($F=5.94$, d.f. 1, 18, $P<0.05$). The AD_{50} values were 0.54 and 0.26 mg/kg for methamphetamine and *p*-chloromethamphetamine respectively.

Fenfluramine, chlorphentermine, cocaine and p-hydroxyamphetamine

The results for one representative dose of each of these drugs are shown in detail in Figure 7. With fenfluramine, clear CTAs were obtained at low doses. For example, consumption of flavours paired with fenfluramine at a dose of 0.63 mg/kg declined progressively over their repeated presentations, whereas the same rats' consumption of saline-paired flavours remained high (Figure 7a). The aversion was significant on both single-stimulus tests ($t=3.63$, d.f. 3, $P<0.05$) and two-stimulus tests ($t=8.94$, d.f. 3, $P<0.01$). At higher doses of fenfluramine, aversions were more marked (e.g. mean flavour intake fell from 17.5 to 3.4 ml after a single pairing with fenfluramine at 2 mg/kg).

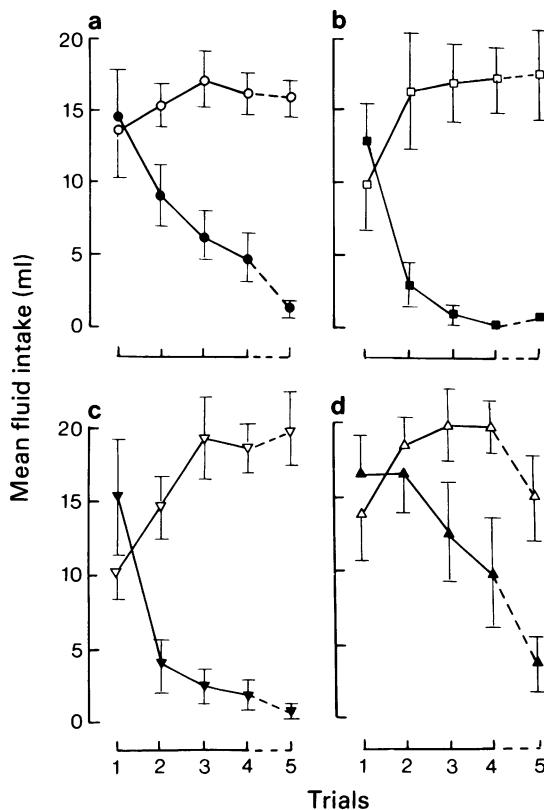


Figure 7 Flavour aversions conditioned in four groups of rats with (a) fenfluramine 0.63 mg/kg, (b) chlorphentermine 10.0 mg/kg, (c) *p*-hydroxyamphetamine 32 mg/kg or (d) cocaine 36 mg/kg. Mean intakes of the drug- and saline-paired flavours are shown by the solid and open symbols respectively ($n=4$).

Clear aversions were also obtained with chlorphentermine, albeit in fairly high doses; Figure 7b shows results for 10 mg/kg, the highest dose tested, which produced significant aversion on both single-stimulus tests ($t=4.45$, d.f. 3, $P<0.05$) and two-stimulus tests ($t=10.3$, d.f. 3, $P<0.01$). It was also necessary to administer large amounts of *p*-hydroxyamphetamine in order to obtain marked aversions. Figure 7c shows the suppressed intake of flavoured solutions after pairings with *p*-hydroxyamphetamine at a dose of 32 mg/kg. At this dose, aversion was significant both on single-stimulus tests ($t=9.64$, d.f. 3, $P<0.01$) and two-stimulus tests ($t=9.36$, d.f. 3, $P<0.01$). In contrast, even very large doses of cocaine produced rather weak aversions. For example, Figure 7d shows that with a dose of 36 mg/kg, a slowly-developing aversion was seen; this

was statistically significant on the single-stimulus tests ($t=5.04$, d.f. 3, $P<0.05$) but not the two-stimulus test ($t=2.91$, d.f. 3).

Dose-response relations for fenfluramine, chlorphentermine, *p*-hydroxyamphetamine and cocaine are shown in Figure 8. Clear dose-response curves were obtained with all these drugs except cocaine. The potency of fenfluramine ($AD_{50}=0.52$ mg/kg) was similar to that of (+)-amphetamine ($AD_{50}=0.47$ mg/kg). A larger dose of fenfluramine (5 mg/kg) than those shown in Figure 8 was also tested and it yielded a mean aversion index of -14.5 (s.e. 2.1) ml/trial, which indicates that the large standard error of the mean aversion index at 2 mg/kg of fenfluramine did not greatly distort the dose-response curve. Since only four rats were tested at each dose, occasional large standard errors were to be expected. The dose-response curves for chlorphentermine ($AD_{50}=3.8$ mg/kg) and *p*-hydroxyamphetamine ($AD_{50}=6.95$ mg/kg) were displaced to the right as compared with those for fenfluramine and amphetamine. However, cocaine was not only of low potency, but also yielded a poor dose-response curve. When the results from all doses of cocaine (2.0, 6.32, 20 and 36 mg/kg) were analysed statistically, significant aversion could be detected on both single-stimulus tests ($F=11.7$, d.f. 1,12, $P<0.01$) and two-stimulus tests ($t=4.91$, d.f. 12, $P<0.001$). Aversion experiments with even larger doses of cocaine (45–63 mg/kg) were not attempted because preliminary tests indicated that transient, clonic convulsions occurred a few minutes after injections.

Discussion

Rats refused to drink a distinctively flavoured solution when its consumption had been followed by injections of amphetamine or one of several related compounds. In the same rats, intakes of flavours paired with saline injections tended to increase over successive presentations and furthermore, when given a choice between two flavours, conditioned rats avoided the drug-paired flavours. Thus, the CTA was specific to the particular flavour which had been paired with the effects of the drug. Even groups of only four rats at each dose, counterbalanced for flavour pairings and sequences, gave reliable results in this discriminative, CTA procedure. It was therefore feasible to use the standardized procedure to quantify differences in potency between different amphetamines in CTA induction. Indeed, the method was sensitive enough to give results with (+)- and (-)-amphetamine which suggested that the relative effectiveness of drugs may be dependent on the time courses of their actions.

With the standard form of our taste aversion procedure, there was virtually no difference between the potencies of (+)- and (-)-amphetamine. (+)-Amphetamine can be several times as potent as (-)-

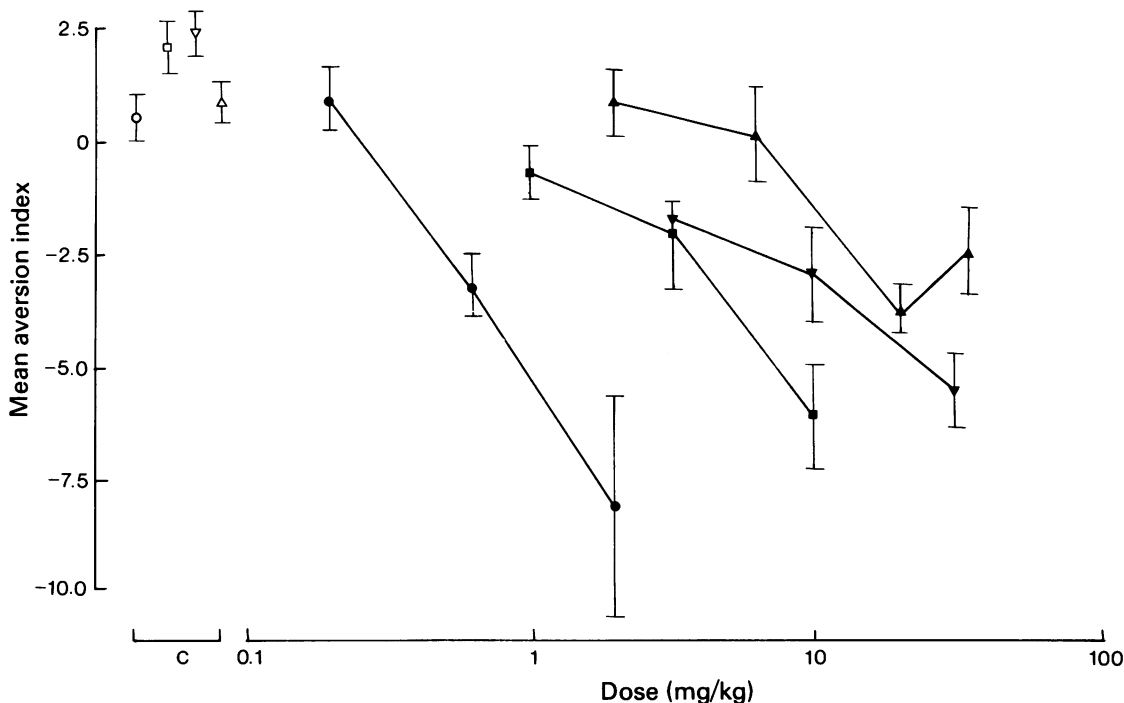


Figure 8 Dose-response curves for flavour aversions conditioned in rats with fenfluramine (●), chlorphentermine (■), *p*-hydroxyamphetamine (▼) and cocaine (▲). Four rats were tested at each dose and the intakes of saline-paired flavours were pooled to provide control data (points above C on abscissa scale).

amphetamine in other behavioural tests (Balster & Schuster, 1973; Baez, 1974; Goodall & Carey, 1975). At one time it was thought that a low potency ratio indicated dopaminergic mediation of behavioural effects of amphetamine (Taylor & Snyder, 1970), but more recent findings have shed doubt on the validity of such interpretations (e.g. Harris & Baldessarini, 1973).

Carey & Goodall (1974) found that (+)-amphetamine was about four times as potent as (-)-amphetamine in CTA in rats. In their procedure, the drugs were injected 15 min after 30 min presentations of saccharin solutions, whereas we administered the drugs immediately after 15 min presentations of fluids. Increasing the interval between ingestion and injection can attenuate flavour aversions (Garcia *et al.*, 1966) and it has also been shown that the locomotor stimulant effects of (-)-amphetamine appear at a later time after injection than those of (+)-amphetamine (Segal, 1975). Temporal factors were therefore a possible source of the discrepancy between our results and those of Carey & Goodall (1974), and the findings of the supplementary experiment with injections delayed by 45 min provided partial support for this hypothesis. Thus it is possible that the different

findings could be completely reconciled by further manipulations of time and dose parameters, although other factors may also prove to be involved.

Taste aversions conditioned with methamphetamine have been described (Martin & Ellinwood, 1974; Goudie & Thornton, 1975; Goudie *et al.*, 1976) and our comparative study showed that *p*-chloromethamphetamine was significantly more potent than the parent compound. These two substances have been found to be approximately equipotent as anorexigenic agents in rats, but *p*-chloromethamphetamine has only about one-tenth of the potency of methamphetamine in facilitating conditioned avoidance behaviour or motor activity (Simon, Larousse & Boissier, 1970; Cox & Maickel, 1972). Their relative potency in CTA experiments may therefore be more closely correlated with anorexigenic potency than with behavioural stimulation. *p*-Chloromethamphetamine (15 mg/kg) can greatly deplete the overall amount of 5-hydroxytryptamine (5-HT) in rat brain (Sanders-Bush, Bushing & Sulser, 1975). It follows that aversions conditioned with methamphetamine and *p*-chloromethamphetamine may involve different neurochemical substrates.

Taste aversions have been conditioned previously in rats with large doses of fenfluramine (Goudie & Thornton, 1975; Goudie *et al.*, 1976). The present experiments confirm such observations and extend them to lower doses. Fenfluramine has anorexigenic potency in rats similar to that of amphetamine, but the two drugs differ in several other ways (Le Douarec & Neveu, 1970). Notably, fenfluramine depresses conditioned avoidance behaviour of rats (Cox & Maickel, 1972) and is not self-administered by rats or rhesus monkeys (Woods & Tessel, 1974; Götestam & Andersson, 1975) and has different subjective effects in man (Griffith, Nutt & Jasinski, 1975). Large doses of fenfluramine can deplete 5-HT in brain (Le Douarec & Neveu, 1970; Clineschmidt, Totaro, McGuffin & Pflueger, 1976; Trulson & Jacobs, 1976), but the significance of this action for CTA remains an open question.

Chlorphentermine induced strong CTA, although the doses required were large compared with those of amphetamine and fenfluramine. However, the anorexigenic potency of chlorphentermine is also lower than that of amphetamine, and it neither facilitated nor depressed conditioned avoidance behaviour over a wide range of doses (Cox & Maickel, 1972). Chlorphentermine also differs from amphetamine in the sense that it has much less stimulating effect on spontaneous motor behaviour (Holm, Huus, Kopf, Nielsen & Petersen, 1960). Chlorphentermine apparently does not deplete brain 5-HT (Dubnick, Leeson, Leverett, Morgan & Phillips, 1963; Nielsen & Dubnick, 1970) and in this respect seems different from fenfluramine.

Our results showed that *p*-hydroxyamphetamine was much less potent than (+)-amphetamine in conditioning taste aversions. *In vitro* experiments have indicated little difference between the effects of these two drugs on the release or uptake of dopamine, noradrenaline and 5-HT by synaptosomes prepared from rat brains (Raiteri, Del Carmine, Bertolli & Levy, 1977). The low aversive potency of *p*-hydroxyamphetamine can therefore be attributed to its presumably poor penetration into the brain, and it follows that central actions may be mainly responsible for amphetamine-induced taste aversions. This conclusion is supported by the observation that intraventricular administration of 6-hydroxydopamine

can attenuate the conditioning of taste aversions with amphetamine (Roberts & Fibiger, 1975).

Cappell & Le Blanc (1975) have reported briefly on a failure to condition taste aversions with doses of cocaine up to 36 mg/kg but Goudie (personal communication) has found cocaine to be weakly active. Although we did obtain statistically significant aversions with cocaine, these effects were very weak compared with those of several other drugs. It was difficult to estimate an AD₅₀ value since the dose-response relationship was poor, but it was obvious that cocaine at 20–36 mg/kg was equivalent to less than 1 mg/kg of (+)-amphetamine. In several other behavioural tests, amphetamine was only about 3–10 times more potent than cocaine (Smith, 1965; Goldberg, 1973; D'Mello & Stolerman, 1977) and therefore, the CTA effect of cocaine seems remarkably weak.

In conclusion, strongly aversive agents may be either powerful (amphetamine, methamphetamine) or weak (fenfluramine, *p*-chloromethamphetamine) behavioural stimulants. Furthermore, cocaine, a powerful stimulant, was a weak aversive agent. Firstly therefore, it appears that the potency of amphetamine congeners in flavour aversion experiments is unrelated to their stimulant potency. The aversive potency of the halogen-substituted derivatives was at least as great as that of the unsubstituted, parent compounds; secondly, aversive potency cannot be correlated with the differential activity of these drugs on catecholaminergic and 5-HT mechanisms. Thirdly, the CTA effect of amphetamine is largely central, since para-hydroxylation greatly weakened conditioning. Fourthly, the time course of drug action in relation to flavour stimulation may be critical; delayed injections differentiated (+)- and (–)-amphetamine whereas low doses failed to do so. Finally, CTA potency seemed to be correlated with anorexigenic activity observed in previous studies. These possible relationships are being investigated further.

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