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Factors Influencing Flavour Aversions Conditioned with Amphetamine in Rats[1]

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D'MELLO, G. D., I. P. STOLERMAN, D. A. BOOTH AND C. W. T. PILCHER. *Factors influencing flavour aversions conditioned with amphetamine in rats.* PHARMAC. BIOCHEM. BEHAV. 7(3) 185–190, 1977. – Rats would not drink distinctively flavoured solutions after their previous ingestion had been followed by injection of amphetamine (1 mg/kg). In the same rats, intake of flavoured solutions followed by saline injections was not suppressed. Providing the rats with cues as to the location of flavoured solutions paired with amphetamine did not alter either the speed of development or the final severity of the aversion. Neither increasing the interval between presentation of the flavour and injection of amphetamine, nor decreasing baseline drinking levels, altered the final degree of aversion. The aversion became progressively weaker as the dose of amphetamine was reduced, but it was detectable at doses as low as 0.1 mg/kg. Further decreases in dose did not enhance intake of flavours paired with amphetamine, even when combined with reductions in baseline drinking brought about by reduced fluid deprivation and flavour palatability. The results are discussed in relation to the conditions in which amphetamine has been shown to exhibit either rewarding or aversive properties.

Amphetamine Flavour aversion Drug dependence CS–US interval

ANIMALS with chronically implanted venous catheters can be trained to press levers to obtain infusions of certain drugs. According to this criterion of self-administration, a number of psychoactive drugs can act as rewards. These drugs include, for both the rat and monkey, opioids [29], central nervous system stimulants [27, 28, 29] and barbiturates [16, 29, 34]. However, there is evidence that drugs which are self-administered can also have aversive properties in other circumstances. For example, Le Magnen [22] found a progressive decrease in the intake of a distinctively flavoured food when its prior consumption was followed by injection of amphetamine. A decrease in intake was also found when amphetamine was added directly to the food [22,26] and similar results have been obtained with oral intake of solutions of amphetamine [8, 15, 32]. Aversive properties of amphetamine have also been reported with procedures modified from Garcia, Kimeldorf and Koelling [14]. In these experiments, aversions to flavoured solutions were induced by injecting amphetamine shortly after the solutions were consumed [5, 9, 18, 24]. Flavour aversions have also been conditioned with many other psychoactive substances, including opioids [7,21] and barbiturates [33]. The finding that pretreatment with α-methyl-para-tyrosine can block both the development of an aversion induced by amphetamine [18] and amphetamine self-administration [11] suggests that the aversive and rewarding properties of amphetamine may be mediated by similar neurochemical systems.

One approach to explaining why a drug may have both rewarding and aversive properties involves analyzing differences between the conditions in which these effects can be demonstrated. The present series of experiments assessed the possible importance of three of these differences, namely position preferences, baseline intake and dose level. A preliminary report of these experiments has been given previously [4].

Exteroceptive stimuli paired with rewarding drugs can also serve as rewards, thus maintaining behaviour which had previously been maintained by drug infusions alone [17]. Thus, during self-administration experiments animals may orientate themselves to a particular location in their immediate environment, such as that of the lever which delivers the drug infusion. Spatial cues were therefore included in the design of one of the experiments.

Secondly, in most flavour aversion experiments, the animals are severely deprived of water. Such animals then drink large amounts during restricted periods of access to highly palatable fluids such as saccharin solutions, and these high intakes might obscure any further increases which would otherwise be induced by a rewarding effect of the drug. It was thought possible that different results might be obtained if the baseline of fluid intake was decreased by reducing the degree of fluid deprivation and by decreasing the palatability of the flavoured solution.

Finally, increasing the interval between the presentation of a flavour (as conditioned stimulus, CS) and injection of drug (as unconditioned stimulus, US) can attenuate aversion [30]. The intensity of flavour aversions decreases with

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TABLE 1

SUMMARY OF FLAVOUR-INJECTION SEQUENCES FOR A TYPICAL GROUP OF 4 RATS IN WHICH FLAVOURS USED WERE 'CHICKEN' AND 'LEMON' (SEE TEXT). DAYS 1 AND 3 REFER TO 1ST AND 3RD DAYS RESPECTIVELY OF EACH 4-DAY CYCLE. DISTILLED WATER WAS MADE AVAILABLE FOR 60 MIN ON DAYS 2 AND 4. HOWEVER, FLAVOURS WERE PRESENTED FOR ONLY 15 MIN AND THEREFORE DISTILLED WATER WAS ALSO PRESENTED ON DAYS 1 AND 3, FOR 45 MIN

	Day 1		Day 3	
Rat	Flavour	Injecton	Flavour	Injection
1	Chicken	Saline	Lemon	Amphetamine
2	Chicken	Amphetamine	Lemon	Saline
3	Lemon	Saline	Chicken	Amphetamine
4	Lemon	Amphetamine	Chicken	Saline

lower doses of amphetamine [6, 10, 24]. Hence, lengthened CS–US intervals and very low doses of amphetamine were used in attempts to condition increased intakes of flavoured solutions paired with the drug.

METHOD

Animals

Male, hooded rats bred in the Department of Psychology, University of Birmingham, and weighing 200–300 g were used. Throughout the experiments all rats were kept in a room maintained at about 22°C and with a regular light-dark cycle (light from 08.00 hr–20.00 hr).

Drugs

(+)–Amphetamine sulphate (Smith, Kline and French or K. and K. Laboratories) was dissolved in isotonic saline and injected intraperitoneally in a volume of 1.0 ml/kg body weight.

Flavoured solutions adapted from previous work [3,23] were prepared by dissolving sodium chloride, monosodium glutamate, citric acid, sodium saccharin or quinine hydrochloride (all from B.D.H. Chemicals, Poole, Dorset), in distilled water.

General Procedure

The procedure was modified from Cappell and LeBlanc [5] to involve discrimination between two flavours. Rats were housed individually in cages to which were attached two calibrated drinking tubes, one either side of the food hopper. Two weeks after the rats arrived in the laboratory, access to water was restricted to one hr per day (10.00–11.00 hr). All rats remained on this regimen for 10 days before the first occasion on which flavours were presented. Fluids were always presented on the left side of the cage unless otherwise specified.

On Days 1 and 3 of a four-day cycle, which was repeated four times, all rats were presented with one of two flavoured solutions for 15 min (single-stimulus tests). Immediately after the solutions were removed, the rats were injected with either amphetamine or saline. For half the rats in an experiment, one flavour was repeatedly followed by amphetamine and the other was followed by saline, and vice versa for the remaining rats. This is summarised in Table 1. The design ensured that any effects due to unconditioned palatability of the flavours and to injection sequence were balanced out in the averaged results. At 16.30–17.15 hr, 6.5 hr after the 15 min presentations of solutions on Days 1 and 3, all rats were allowed access to distilled water for 45 min ('supplementary water'). This ensured that all rats had a total of 1 hr access to fluid each day.

When the four-day cycle had been repeated four times, injections were discontinued and on the following day, all animals were allowed access to distilled water from 10.00–11.00 hr as usual. During the subsequent two days, all animals were presented with both flavours simultaneously for 15 min (two-stimulus tests). On the second two-stimulus test, the positions of the flavours were reversed to control for side preferences. The mean intake of each flavour was then calculated for each rat. After each two-stimulus test, 'supplementary water' was presented as above.

Throughout all experiments the minimum number of rats used in each group was four, but in some experiments the whole procedure was replicated in four additional rats.

Statistical Analyses

Strong taste aversions can produce different variances in control and experimental data, which may therefore violate the assumptions of analyses of variance. In order to minimise this problem, the rates of change (linear regression coefficients) of flavour intake over Trials 1–4 were computed for each animal. Using these coefficients as indices of aversion, *t*-tests, single-factor or two-factor analyses of variance were performed, utilizing repeated measures where appropriate [35]. Rapid development of extreme aversion after only one or two trials causes deviations from linearity so that regression coefficients calculated as described above become misleading; therefore, when averaged 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 (Trial 5), the percentage of the total fluid intake consumed as the flavour previously paired with drug was calculated. Then *t*-tests were carried out to determine whether the mean scores differed significantly from 50%. The percentage scores were subject to arc-sin transformations as is customary for such data [35].

EXPERIMENT 1: EFFECTS OF SPATIAL CUE, CS-US INTERVAL AND DECREASED BASELINE DRINKING

Method

Twenty-four rats were allocated to six groups (n = 4) using a randomization procedure to form a two-factor (2 × 3) design. The flavours were chicken (sodium chloride, 40 mM; monosodium glutamate, 40 mM) and lemon (citric acid, 1.0 mM; sodium saccharin, 2.0 mM). Groups 1, 3 and 5 received only the flavour cues whereas Groups 2, 4 and 6 received spatial as well as flavour cues paired with drug injections; spatial cues were provided by ensuring that the flavour followed by drug injection was always placed on the right side of the cage whereas the saline-paired flavour was always on the left. The procedures for Groups 1 and 2 did not otherwise deviate from the general procedure. For Groups 3 and 4, injections were delayed for 45 min after the end of the flavour presentation, thereby increasing the CS–US interval. For Groups 5 and 6 the degree of fluid deprivation was reduced by allowing access to a predetermined amount of water from 16.15 hr on each evening

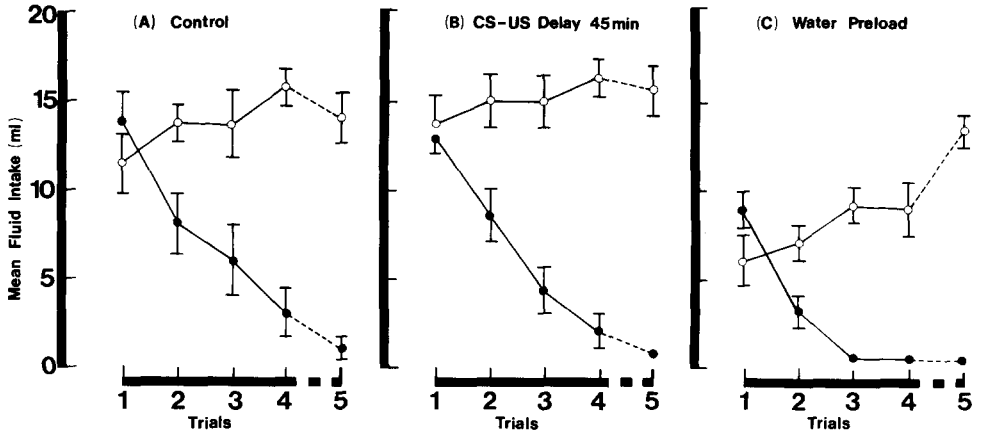

FIG. 1. (A) Progressive decrease in intake of flavours paired with amphetamine at 1.0 mg/kg as compared with flavours paired with saline. (B) Lack of effect of increasing the CS–US interval on aversion conditioned with amphetamine (1.0 mg/kg). (C) Development of aversion after decreasing the degree of fluid deprivation by giving water loads before flavour presentations (except Trial 5). (●——●) amphetamine-paired flavours; ○——○ saline-paired flavours). Each point represents the mean of the results from 8 rats. Vertical bars show ± 1 SEM.

prior to a flavour presentation. This water load consisted of 75% of the mean intake of distilled water during the 1 hr periods of access prior to the first flavour presentation, and it was normally consumed within 1–2 hr. In preliminary experiments this procedure was found to decrease the fluid intake on the following day by about 50%. Amphetamine was injected at a dose (1.0 mg/kg) known to induce reliable flavour aversions in rats [6].

Results

Interactions between the treatments applied to different groups were not statistically significant and so the pooling of certain groups was permissible to facilitate evaluation of the main effects of the factorial design. The results averaged to show any effects of increasing the CS–US interval or of the water loads are shown in Fig. 1. There was no significant difference between the initial intakes (Trial 1) of the amphetamine- and saline-paired flavours. On Trial 2, there was a decrease in the intake of those flavours which had been paired with amphetamine on Trial 1, as compared with intake of saline-paired flavours. Further decreases were seen during Trials 3 and 4. Differences between the aversion indices of amphetamine- and saline-paired flavour intakes proved significant throughout (Fig. 1(A): $F = 32.6$; Fig. 1(B): $F = 47.1$; Fig. 1(C): $F = 15.0$; df 1, 6: $p<0.01$ in all cases). However, neither increasing the interval between presentation of flavour and injection of amphetamine (Fig. 1(B)) nor decreasing the degree of deprivation (Fig. 1(C)) affected the flavour aversion, although the latter manipulation had the desired effect of reducing the baseline by approximately 50%. In order to simplify comparison with other groups, Groups 5 and 6 did not receive the water load prior to Trial 5 (two-stimulus tests); thus it can be seen from Fig. 1(C) that the final degree of aversion to amphetamine-paired flavours was not diminished by previous water loading. When animals drank small amounts of flavoured solutions (Trials 2, 3 and 4), intake during the supplementary water presentations tended to increase; differences in intake between water after drug-paired flavour and water after saline-paired flavour were highly significant, $F(1,18) = 20.3$, $p<0.001$. This compensatory increase persisted to the following day and remained significant [4]. Conditioned taste aversions also developed to about the same extent regardless of whether flavour cues only or flavour and spatial cues were presented. The mean aversion indices in these two conditions were −4.2 and −3.6 ml trial^{-1} respectively ($F< 1$ df 2, 18).

In four additional rats, an attempt was made to pair the drug effect more closely in time with flavour ingestion, thus making the contingencies closer to those in self-administration experiments. For these rats, amphetamine (1.0 mg/kg) was injected 5 min after the start of 15 min flavour presentations. The percentage of the total fluid intake consumed as the amphetamine-paired flavour during the two-stimulus tests was then 8.5 ± 1.5% (mean ± SE), as compared with 6.7 ± 1.5% for the standard procedure. Strong flavour aversion therefore developed despite this variation in the time of injection.

EXPERIMENT 2: DOSE–RESPONSE RELATIONS

Method

In this experiment the effects of four doses of amphetamine (0.032, 0.10, 0.32 and 1.0 mg/kg) were determined (n = 8 per dose). The general procedure was followed throughout except that half the rats at each dose level received the same flavours as were used in Experiment 1 and half received a modified chicken flavour (sodium chloride, 128 mM; monosodium glutamate, 12.5 mM). There were no detectable differences in intake between the modified and original chicken flavours and, therefore, the data were pooled. Four rats receiving amphetamine at 1.0 mg/kg in Experiment 1 were included as part of the group of eight rats receiving that dose in Experiment 2.

Results

The effects of four doses of amphetamine can be seen in Fig. 2. Intake of those flavours paired with amphetamine at 1.0 mg/kg decreased progressively over the four trials. Intake of the saline-paired flavours remained relatively constant and the difference in aversion index between the two flavours was highly significant ($t = 4.53$, df 7, $p<0.01$). The much greater intake of the saline-paired flavours as compared with the amphetamine-paired flavours during the two-stimulus tests confirmed the aversion to the latter ($t = 16.6$, df 7, $p<0.001$). At a dose of 0.32 mg/kg (Fig.

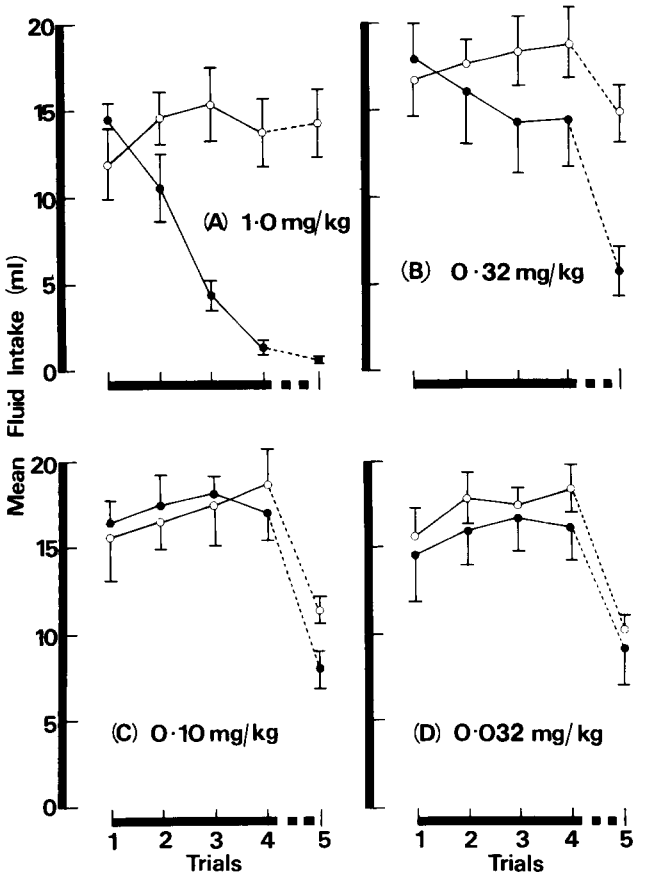

FIG. 2. The effect of varying the dose of amphetamine on the development of flavour aversion. (●——● amphetamine-paired flavours; ○——○ saline-paired flavours, n = 8 at each dose.)

2(B)), the aversion was not as severe, but was significant both on single-stimulus (t = 2.72, df 7, $p<0.05$) and two-stimulus tests (t = 3.18, df 7, $p<0.05$). However, at the lower doses (0.10 and 0.032 mg/kg, Fig. 2(C) and (D), there were no significant differences between the aversion indices for the amphetamine- and saline-paired flavours over Trials 1–4. A small but significant aversion for the flavour paired with amphetamine at 0.10 mg/kg was detected in the two-stimulus tests (t = 2.74, df 7, $p<0.05$). This result is consistent with an increased sensitivity of the two-stimulus tests over the single-stimulus tests, because animals can maintain normal fluid intake while avoiding an aversive flavour [19, 22, 37].

Aversion indices calculated from the results of the single-stimulus tests for both drug- and saline-paired flavours are plotted against dose in Fig. 3(A), whereas Fig. 3(B) summarizes the results from the two-stimulus tests. The tendency for the animals to avoid the drug-paired flavour, and for this avoidance to increase with dose is clearly seen, indicating strong dose-response relations for both single- and two-stimulus tests.

EXPERIMENT 3: EFFECT OF VERY LOW DOSES

Method

Sixteen rats were randomly allocated to four groups (n = 4), forming a two-factor (2 × 2) design. Amphetamine was tested at doses of 0.025 mg/kg (Groups 1 and 2) and 0.05 mg/kg (Groups 3 and 4). The general procedure was followed for Groups 1 and 3. For Groups 2 and 4, the degree of fluid deprivation was reduced by water loads as described for Experiment 1. The flavours used were lemon (citric acid, 1.0 mM; sodium saccharin, 1.0 mM) and tonic (quinine hydrochloride, 0.02 mM; sodium saccharin, 1.0 mM).

Four additional groups (n = 4) comprised a further 2 × 2 design which was used to explore the influence of further decreases in palatability and an even lower dose of amphetamine (0.01 mg/kg). Two groups received the lemon and

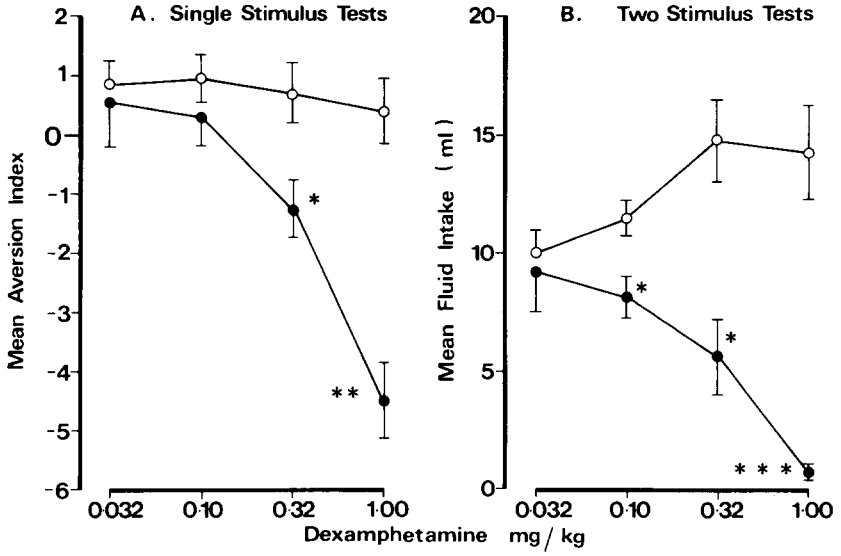

FIG. 3. (A) Aversion indices (see text) for drug- and saline-paired flavours at four doses of amphetamine (n = 8). (B) Mean 15 min flavour intakes during simultaneous presentations of both amphetamine- and saline-paired flavours (n = 8).(●——● amphetamine-paired flavours; ○——○ saline-paired flavours; *$p<0.05$; **$p<0.01$; ****$p<0.001$.

tonic flavours referred to above and one of these groups also received the water loads to reduce fluid deprivation. The remaining two groups received a more acidic lemon flavour (citric acid, 4.0 mM; sodium saccharin, 1.0 mM) and a more bitter tonic flavour (quinine hydrochloride, 0.10 mM; sodium saccharin, 1.0 mM); one of these two groups also received water loads.

Results

Pairings with amphetamine (0.025 mg/kg and 0.05) produced neither preferences nor aversions for flavoured solutions. Over the four single stimulus tests (Trials 1–4), there were no significant differences between the aversion indices calculated for drug- and saline-paired flavours at either dose level. These negative results are not described in detail; in general, the differences between the mean intakes of the drug- and saline-paired flavours were not greater than those at a low dose in the previous study (Fig. 2(D)). Thus, providing less palatable flavours and giving amphetamine at low doses, both with and without water loads, did not induce any significant differences between intakes of amphetamine- and saline-paired flavours. Finally, the attempt to induce an enhanced intake of an amphetamine-paired flavour using the very low dose of 0.01 mg/kg in combination with less palatable flavours and water loads also failed. For example, in the two-stimulus tests the percentage of the total fluid intake consumed as the flavour paired with amphetamine (0.01 mg/kg) was 46.9 ± 7.0% (mean ± SE), which does not differ significantly from 50%.

DISCUSSION

It is well known that amphetamine has rewarding properties which can be demonstrated by the usual self-administration techniques [27–29]. The present experiments confirm that even very small doses of amphetamine have aversive properties which can be detected in flavour intake experiments [22]. Aversions were induced in rats at doses of amphetamine from 0.10 to 1.0 mg/kg, thus covering much of the dose range known to be self-administered [12,28]. Even smaller unit doses (e.g., 0.015 mg/kg) are also self-administered [11], but produced neither preference nor aversion in our experiments. Taste aversions were specific to the drug-paired flavours, thus excluding a more general sensitisation or enhancement of neophobia as an alternative explanation [1]. The contrasting aversive and reinforcing effects of amphetamine presumably reflect differences in the experimental procedures used to demonstrate them; by combining both procedures in a single experiment, Wise and his coworkers have shown that self-administered doses of apomorphine can also produce flavour aversions in the same rats [36].

Exteroceptive cues presented contiguously with drug infusions may become conditioned reinforcers [17], and consequently may play a role in the mediation of rewarding effects of drugs during self-administration experiments. However, the addition of spatial cues in Experiment 1 did not affect the development of aversion with amphetamine. The factors which may have contributed to this negative finding include differences in saliency of flavour and spatial cues, the possible difficulty in discriminating between the two sides of the cage, and the initial spatial preferences of the animals prior to conditioning, which may have been too strong to be shifted [25]. As all drinking prior to conditioning took place on the left side of the cage, and drug-paired flavours were always presented on the right, the last suggestion seems most plausible. Randomly varying the positions of all tubes before the first flavour presentation might have circumvented this difficulty. However, Martin and Ellinwood have also failed to influence flavour aversion by spatial manipulation of a rather different nature [25].

The degree of aversion to flavours paired with amphetamine (1 mg/kg) was not affected by delaying injections for 45 min after flavour presentations (Fig. 1(B)). In other experiments, attenuation of flavour aversion by increasing the CS–US interval has been demonstrated [30] and failure to obtain an effect in the present experiment may indicate that a 45 min interval was too brief. Injection of amphetamine during drinking trials also resulted in strong aversion. In some circumstances reduced intake of a flavoured solution can weaken conditioning [2], but such an affect was not seen in the present experiments when intake was reduced by water loading.

Lower doses of amphetamine (0.1–0.32 mg/kg) yielded weaker aversions (Figs. 2 and 3). If amphetamine becomes rewarding instead of aversive as the dose is decreased, this should have been detected in Experiments 2 and 3; however, even when very low doses of amphetamine were used in combination with less palatable flavours and reduced fluid deprivation, no enhancement of flavour intake was obtained. The shape of the dose-response curve (Fig. 3) also suggests that there was little chance of further dose variations being sufficient to enhance intake. Other differences between typical self-administration and flavour aversion paradigms include the route of drug administration, control over frequency of drug administrations and type of response.

In the majority of self-administration experiments drugs have been infused through a venous catheter, whereas in the experiments which show aversion the intraperitoneal route has been used most often. However, Wise *et al.* [36] have shown that substantial aversions can occur when either amphetamine or apomorphine is given intravenously. On the other hand, the self-administration of morphine using the intraperitoneal route has also been demonstrated [20]. As the taste aversion paradigm is capable of revealing rewarding effects when vitamins are injected intraperitoneally [13], it becomes difficult to maintain that differing routes of administration determine whether the rewarding or aversive properties of amphetamine take precedence.

Secondly, it has been suggested that the animal's control of the rate at which stimuli are received may be important in determining their reward value [31]. This principle may also apply to drug self-administration experiments during which an animal typically has considerable control over the frequency of drug infusions. This does not apply during flavour aversion experiments where a single, relatively large dose is given by the experimenter at a predetermined time. However, there are instances reported where the animal does have control over the frequency of drug administrations and yet the drugs have proved aversive [8, 32, 36]. Other reports have demonstrated the converse [11,17].

Thirdly, differences in the type of response used by the animal in self-administration and flavour-aversion paradigms may also be relevant to the problem. For example, work is now under way in our laboratory to determine whether flavour aversions to amphetamine can be expressed by an operant response such as bar-pressing.

Finally, Carey and Godall [9] have shown that ampheta-

mine (1 mg/kg IP) can decrease water intake when administered prior to drinking sessions. The possibility exists therefore that flavour aversions develop because, after the initial flavour-drug pairing, the taste of the flavoured solution elicits the drug's anorexigenic effect. Work is in progress to see whether the potency of amphetamines in flavour aversion experiments can be correlated with their anorexigenic or adipsogenic properties.

In the light of the present findings, it seems that several of the differences between self-administration and flavour aversion experiments are not sufficient to explain why amphetamine appears rewarding in one context and aversive in another. That a drug should have different effects in different circumstances is not remarkable, but such an explanation, while very likely correct, is inadequate since it has no predictive power unless the critical factor or factors can be identified. The robustness and reproducibility of both the rewarding and the aversive properties of amphetamine suggest that this problem should be investigated further.

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