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BRIEF COMMUNICATION

Effects of Prior Drug Experience on the Establishment of Taste Aversions in Rats

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GOUDIE, A. J., M. TAYLOR AND H. ATHERTON. *Effects of prior drug experience on the establishment of taste aversions in rats.* PHARMAC. BIOCHEM. BEHAV. 3(5) 947–952, 1975. – Groups of food and water deprived rats were injected with either 2 mg/kg d-amphetamine, 9 mg/kg dl-fenfluramine or isotonic saline immediately after the first presentation of a 25 percent solution of condensed milk for a 30 min period. When animals were tested for aversion to condensed milk 8 days later both drugs were found to cause a highly significant decrease in total amounts drunk; in contrast saline injected animals showed significant increases in the amount drunk. However, it was found that the development of a conditioned taste aversion could be markedly attenuated or abolished altogether by providing groups of animals with experience of both drugs prior to aversion establishment, and that the degree of attenuation of aversion was proportional to the amount of prior experience. Novelty of drug administered would seem to be a critical variable in the establishment of taste aversions. The results are discussed with reference to some of the paradoxical aspects of drug induced taste aversions.

Conditioned taste aversions Amphetamine Fenfluramine Prior drug experience Aversive tolerance Self administration

THE phenomenon of conditioned taste aversion has received considerable attention in recent years because of the theoretical problems it raises for traditional learning theories [22, 23, 24, 25]. Three types of treatment administered after ingestion of food can induce pronounced aversion to that food on subsequent exposure. Firstly, the administration of X-ray irradiation [8]; secondly, the administration of substances which are emetics in humans and assumed to be toxic in animals, such as lithium chloride [16], apomorphine [7], and cyclophosphamide [6]; and thirdly, the administration of a wide range of drugs at subtoxic doses including amphetamine [1, 2, 5], mescaline [2], PCPA [17], chlorpromazine [1], scopolamine [1], lorazepam [1], and morphine [4]. This report is concerned with the third class of treatments. Namely, the administration of psychoactive drugs at subtoxic doses.

From a pharmacological viewpoint the demonstrations that administration of these drugs can cause specific food aversions raises two problems. Firstly, the compounds listed above include representatives of almost all the major classes of psychoactive drugs including stimulants, depressants, narcotic analgesics, anxiolytics and neuroleptics. A very wide range of compounds, differing considerably in their basic pharmacological properties, would all seem to possess aversive properties. Secondly, some of these compounds are known to act as reinforcers in self-administration situations (e.g. morphine and amphetamine). It has been shown that d-amphetamine is aversive in the conditioned taste aversion paradigm, at the same dose at which it is self-administered [2,3]. The apparent paradox that the same dose of a drug can have both aversive and reinforcing properties in different situations has been cited as an example of the importance of the experimental procedure involved in determining the effect of a reinforcer [3] and an analogy drawn between this effect and reports that, under specific conditions, electric shock can be positively rewarding [15].

It is undoubtedly true that the exact relationship between responses and stimuli determines subsequent behaviour. However, it is suggested that an examination of the differences between the self-administration situation and

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the taste aversion paradigm is required for an adequate explanation of this apparent paradox. One such difference is that in the former case, drugs are (self) administered chronically (i.e., more than one administration is given), while in the latter they are administered acutely. It is suggested that in humans many psychoactive drugs may have unpleasant initial (acute) side effects which are attenuated after chronic administration. In this report, evidence is presented that provides an analogue of this effect in rats. Specifically, it is shown that prior experience of either amphetamine or fenfluramine prevents the development of a conditioned taste aversion to an extent proportional to the degree of prior experience. It is suggested that perhaps all psychoactive drugs might act as aversive stimuli, but that aversive tolerance develops with chronic administration at a rate dependent upon both the drug involved and dose administered and that the rate of development of this tolerance may be related to the abuse potential of certain drugs. The apparent paradox that amphetamine can be both an aversive stimulus and a reinforcing one at the same dose may consequently not be simply due to differences in the experimental procedures used, but more specifically to the dimension of acute versus chronic administration.

METHOD

Fifty-six male Wistar albino rats, supplied by the U.C.N.W. Zoology Department, weighing between 250 and 350 g at the start of the experiment were used. They were randomly divided into 7 experimental groups and housed in groups of threes. All animals received 3 days training to drink water from a drinking spout located on the roof of a wire mesh cage of dimensions 10 X 11 X 8 in. This pretraining was conducted for 30 min periods at appropriate times throughout the day after the animals had been food and water deprived for 23 hr. Subsequently, animals were given unlimited access to food and water in their home cages and received (x) injections of either d-amphetamine sulphate or dl-fenfluramine hydrochloride at doses of 2 and 9 mg/kg IP respectively. (These doses are approximately equipotent anorexically in rats [11]). Injections were administered daily, at a volume equivalent to 2 ml/kg body weight. The value of (x) was 0, 1, 4 or 8 days for the different experimental groups. Two days after the last injection, or the last training day, whichever was appropriate, animals were food and water deprived, and the next day, (Aversion Establishment Day), placed in the experimental cage with a 25 percent by volume solution of sweetened condensed milk in water in the drinking tube. Immediately after a 30 min drinking period the amount drunk for each animal was recorded, animals injected with the relevant solution, and then again given unlimited access to food and water in their home cages. Eight days later they were again food and water deprived and the next day (Aversion Test Day) presented with condensed milk in the experimental chambers for 30 min, the amounts drunk once more being recorded. The 7 experimental groups were made up as shown in Table 1. Any one experimental group received only one drug throughout the experiment.

RESULTS

The mean amounts drunk for each of the experimental groups on both the Aversion Establishment Day and Aversion Test Days are shown in Fig. 1. For convenience experimental groups which received amphetamine are shown in Fig. 1A and those which received fenfluramine are shown in Fig. 1B, the saline control group being presented twice.

A one way analysis of variance on amounts drunk on the Aversion Establishment Day for the 4 groups shown in Fig. 1A (amphetamine animals plus controls) showed that there were no significant differences between the 4 groups, $F(3,28) = 0.813$, $p = 49\%$; a similar analysis of variance for

TABLE 1

EXPERIMENTAL PROCEDURE

Group	No. of Days of Prior Experience of Injection (x)	Drug Injected on Aversion Establishment Day and on Prior Experience Day(s)
Salines	Zero	Saline
Naive Amphetamine	Zero	Amphetamine
Once Prior Amphetamine	Once	Amphetamine
Four Times Prior Amphetamine	Four Times	Amphetamine
Naive Fenfluramine	Zero	Fenfluramine
Four Times Prior Fenfluramine	Four Times	Fenfluramine
Eight Times Prior Fenfluramine	Eight Times	Fenfluramine

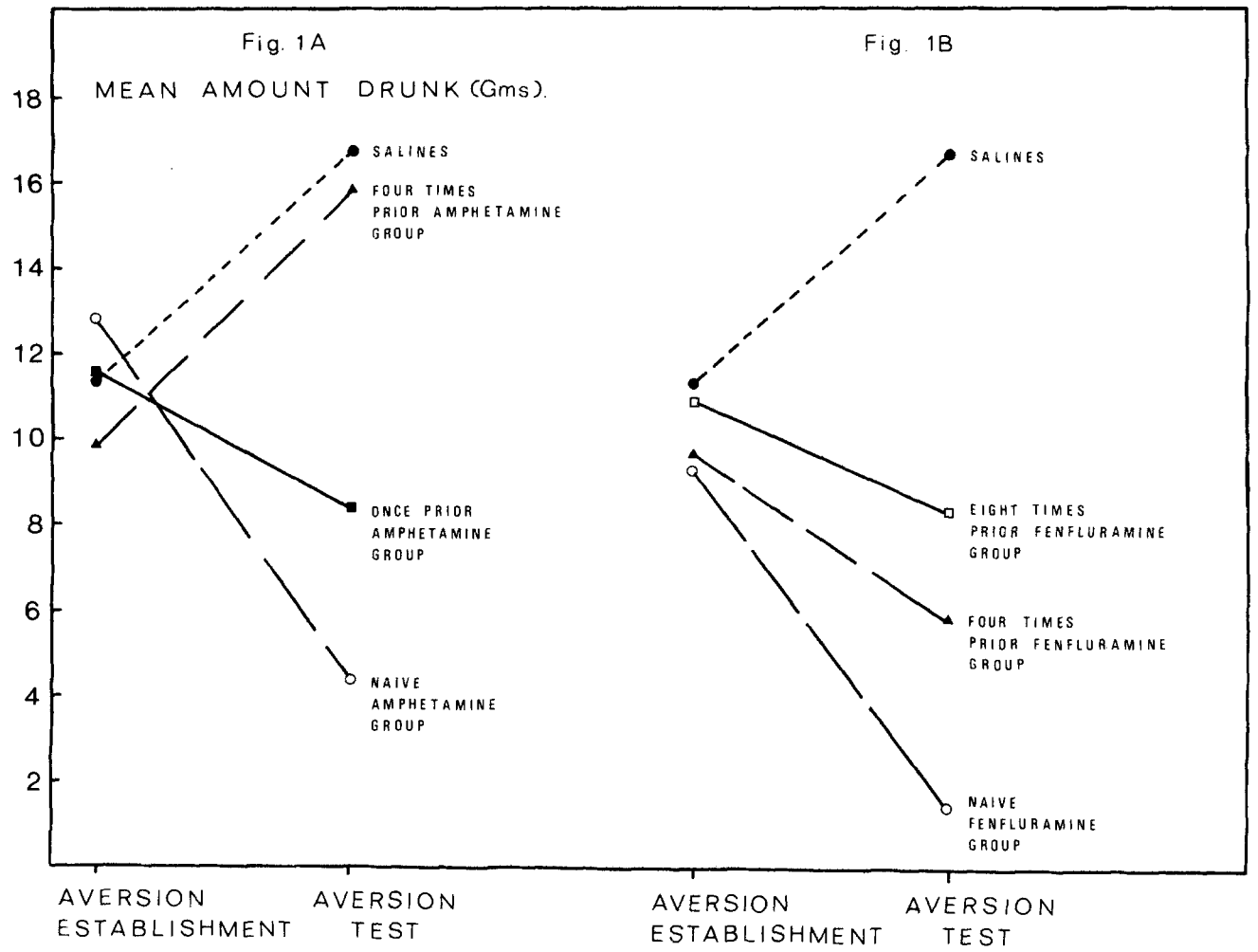

FIG. 1. Mean amounts drunk on aversion establishment and test days after amphetamine (1A) or fenfluramine (1B) administration, under conditions of 1 and 4 days prior amphetamine experience, and 4 and 8 days prior fenfluramine experience.

the 4 groups shown in Fig. 1B (fenfluramine animals plus controls) again illustrated the lack of any significant differences between groups, $F(3,28) = 0.486$; $p = 69\%$, while an overall analysis of variance on amounts drunk for all 7 experimental groups on the Aversion Establishment Day also illustrated the lack of any significant difference between the groups, $F(6,49) = 1.014$, $p = 43\%$. It is clear that the 7 experimental groups are drawn from a homogeneous population of animals. Since it was found in a pilot study during training that there was a significant correlation between body weight and amount of water drunk, a version of Student's t test designed for correlated pairs of observations was used for data analysis. Table 2 shows the results of this analysis. Table 3 shows the results of comparisons between amounts drunk by the various groups on Aversion Testing. It is clear that the magnitude of the aversion diminishes as a function of the degree of prior drug experience at a rate dependent upon the drug used. No differences in relative or absolute body weights were apparent between the groups during the experiment.

DISCUSSION

The results show that both amphetamine and fenfluramine injections can cause the establishment of specific food aversions. The phenomenon appears to be exceptionally strong, and easily replicable when relatively high doses of drugs are used, as in this study, so that it is not always necessary to use the more sensitive two choice method of studying conditioned aversions [12]. The results obtained with d-amphetamine injected naive animals confirm earlier findings [1, 2, 3, 4] as do those obtained with fenfluramine injected naive animals [18]. These results also show that it is possible to establish conditioned taste aversions, using identical procedures, with compounds that differ markedly in their acute behavioral [11] and neurochemical [9] effects.

It is clearly possible to attenuate or abolish the aversive effects of both drugs by providing prior experience of the drug in question. The degree of attenuation of the effect of any particular drug seems to be dependent upon the amount of prior experience of that drug, since there were significant differences in the amounts drunk on Aversion Testing between most of the groups that had received either drug (Table 3), despite the fact that the amounts drunk on Aversion Establishment Days were not signifcantly different.

The fact that saline injected controls drank more on

TABLE 2

EFFECTS OF DRUG INJECTIONS ON AVERSION ESTABLISHMENT DAY ON AMOUNTS DRUNK BY THE VARIOUS GROUPS ON AVERSION TESTING (CORRELATED ONE TAILED *t*-TESTS FOR EACH GROUP)

Groups	Significance Level	Direction of Change
Salines	$p<0.05$	Increase
Naive Amphetamines	$p<0.01$	Decrease
Once Prior Amphetamines	$p<0.05$	Decrease
Four Times Prior Amphetamines	$p<0.01$	Increase
Naive Fenfluramine	$p<0.001$	Decrease
Four Times Prior Fenfluramine	$p<0.01$	Decrease
Eight Times Prior Fenfluramine	Not Significant	–

Aversion Testing than on their first exposure to condensed milk may be explained in terms of a general tendency of rats to restrict intake of novel foods. A similar effect with saccharin as a novel food has been reported [5]. The same increase was noted in the Four Times Prior Amphetamine Group, suggesting that such prior experience totally abolishes any aversive effect of d-amphetamine; but not in the Eight Times Prior Fenfluramine Group in which the aversive effect appears to be attenuated, but not totally abolished.

It seems possible that almost all psychoactive drugs can act as aversive stimuli in this paradigm. Since human subjects receiving psychotropic drugs frequently report unpleasant initial side effects which are reduced by continued experience of the drug, it is suggested that the concept of Aversive Tolerance may be of use in the understanding of behavioural effects of drugs. It is known that development of tolerance to different aspects of a drug's effects on behaviour can occur at different rates [14]. Tolerance to the aversive effects of a drug may develop independently of the development of other types of tolerance. The procedure outlined here provides a relatively sensitive method of determining the rate of development of Aversive Tolerance in rats, which may be one determinant of the likelihood of any particular drug being self-administered. The more rapidly such tolerance develops, the more likely animals may be to self administer the drug in question.

In the light of the results presented above it does not appear surprising that d-amphetamine can act as a reinforcer in a self-administration situation, which essentially involves chronic drug experience, while it can be an aversive stimulus when given acutely in conditioned taste aversion paradigms. The apparent paradox may not be due to differences in the two procedures per se, as has been suggested [3]; but rather to the fact that they differ in terms of the dimension of acute versus chronic administration. It is significant that the aversive effects of the high dose (2 mg/kg IP) of d-amphetamine used here are attenuated after very little prior experience, this being a dose which is known to be self-administered in rats [20].

Self-administration of amphetamine has been reported to be dose dependent, comparatively low self-infusion rates being observed with high doses (around 2 mg/kg); and it has been suggested that this "may reflect in part a punishing component of drug administration" [19]. Similarly, forced injections of d-amphetamine have been found to delay acquisition of self-administration, "suggesting that such injections may be aversive" [21]. The hypothesis that the initial stages of self-administration may involve an aversive component is supported by reports that on CRF schedules of self-administration responding is infrequent and irregular on the first few days [21]; and by reports that some rats will not self-administer d-amphetamine [19]. A similar effect has been reported with rats responding for medazepam [10], and it has been noted that "a small number of subjects do not press the lever very often in the initial days of the experiment, so that self-administration does not occur until later in these rats."

All these findings suggest that the initial stages of self-administration might involve an aversive element. However, it is possible to devise alternative explanations for all the features of the self-administration paradigms outlined above, and they consequently provide only indirect support for the hypothesis. It is logically impossible to show that a particular stimulus can simultaneously have reinforcing and aversive effects on a specified response in a given situation. However, while acknowledging this conceptual problem, it is suggested that the development of stable rates of self-administration requires the development of Aversive Tolerance.

The importance of novelty of food in the establishment of a conditioned taste aversion has been noted [13]; the results reported here indicate that the novelty of drug administered may be an important variable to be considered

TABLE 3

COMPARISONS BETWEEN AMOUNTS DRUNK BY EXPERIMENTAL GROUPS ON AVERSION TESTING (*t*-TESTS)

Groups	Significance Level
AMPHETAMINE	
Salines compared to Naive Amphetamine	$p<0.005$
Salines compared to Once Prior Amphetamine	$p<0.05$
Salines compared to Four Times Prior Amphetamine	Not Significant
Four Times Prior Amphetamine compared to Naive Amphetamine	$p<0.005$
Four Times Prior Amphetamine compared to Once Prior Amphetamine	$p<0.05$
Once Prior Amphetamine compared to Naive Amphetamine	Not Significant
FENFLURAMINE	
Salines compared to Naive Fenfluramine	$p<0.005$
Salines compared to Four Times Prior Fenfluramine	$p<0.005$
Salines compared to Eight Times Prior Fenfluramine	$p<0.05$
Eight Times Prior Fenfluramine compared to Naive Fenfluramine	$p<0.01$
Eight Times Prior Fenfluramine compared to Four Times Prior Fenfluramine	Not Significant
Four Times Prior Fenfluramine compared to Naive Fenfluramine	$p<0.01$

in the taste aversion paradigm. As such, the results form part of a growing body of evidence that prior drug experience has a profound effect on drug actions on behavior [26].

A number of theoreticians [23,25] have suggested that the conditioned taste aversion paradigm is in some way a unique learning situation in that animals are innately predisposed to associate food intake with subsequent illness after one exposure to the treatment causing illness. However, if the analysis proposed in this paper is correct, then it is in no way paradoxical that drugs which are self-administered can act as aversive stimuli in the conditioned taste aversion situation. Explanation of the apparent paradox does not necessarily require the postulation of a unique learning situation; it may be that the aversive effects of self-administered drugs are very rapidly attenuated in a chronic situation with development of Aversive Tolerance, after which such drugs may become positively rewarding.

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