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TOLERANCE PATTERN OF THE ANOREXIGENIC ACTION OF AMPHETAMINES, FENFLURAMINE, PHENMETRAZINE AND DIETHYLPROPION IN RATS

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1 The tolerance pattern to anorectic drugs was studied in starved rats by measuring two consecutive 2 h food intakes.

2 There was a reduction in the first 2 h food intake with development of complete tolerance after fenfluramine and phenmetrazine, and of partial tolerance after amphetamine, (+)-amphetamine and diethylpropion.

3 During the second 2 h intake, the anorectic effect was transient after fenfluramine and diethylpropion; while there was an absolute increase in the intake after amphetamine and (+)-amphetamine.

4 A pair-feeding experiment revealed that the increase in the second 2 h food intake was not a direct effect of the drug but a consequence of the deficit in food intake during the preceding 2 hours.

5 There was an overall correlation between the food and water intake.

6 A significant loss in body weight was observed after amphetamine, fenfluramine and phenmetrazine but not after (+)-amphetamine or diethylpropion.

7 The results indicate that so-called tolerance to the anorexigenic effect of drugs is apparent rather than real and that the duration of food access is a determining factor. The body weight changes may be brought about by the metabolic effects of these drugs rather than their effect on food and water intake.

Introduction

Duration of food access as a determinant of the development of tolerance to the anorectic effect of amphetamine on repeated administration has been demonstrated in starved rats (Ghosh & Parvathy, 1973b). The anorectic effect was found to be restricted to the first 2 h with little evidence of tolerance, while there was an absolute increase in the second 2 h food intake. Blundell, Campbell, Lesham & Tozer (1975) have reported a short appetite suppressant effect following single administration of (+)-amphetamine consistent with the rapid clearance of the blood concentration in deprived rats.

In the present paper, we have analysed the effect of repeated administration of a few other known anorectic drugs in relation to food access as well as to body weight. In addition, an attempt has been made to discover the mechanism by which amphetamine produces an absolute increase in the second 2 h food intake. Some of the preliminary results were presented at the XXVI International Congress of Physiological Sciences, New Delhi (Parvathy & Ghosh, 1974).

Methods

Male albino rats (109–258 g) were housed individually in metabolism cages for three weeks in an ambient temperature between 28–32°C and subjected to a 16 h-dark–8 h-light cycle daily. They were fasted throughout (water allowed *ad libitum*) except for a period of 4 h at a fixed time each day when they were offered a weighed quantity of food pellets (Hindlever) and a measured quantity of water. The food and water consumed during the first and second 2 h periods were measured daily to the nearest 0.1 g and 0.5 ml respectively and recorded on the daily body weight basis. The body weight was measured daily to the nearest 1 g before offering food. In the first (pretreatment) week the animals were stabilized with regard to the food and water intake. At the beginning of the second (treatment) week groups of rats were randomly allocated to one of the following treatments: control—0.9% w/v NaCl solution (saline); amphetamine 5 mg/kg; (+)-amphetamine 2.5 mg/kg; fenfluramine 10 mg/kg; phenmetrazine 25 mg/kg and diethylpropion 10 mg/kg. The daily body weight was

Table 1 Effect of different anorexigens on 4 h food intake in fasted rats

Treatment	Dose (mg/kg)	No. of animals	Pre-treatment week*	4 h food intake g/100 g body weight (mean ± s.e. mean) Treatment week days						
				1	2	3	4	5	6	7
Control (saline)	—	6	4.3 ± 0.6	5.8 ± 1.2	5.5 ± 0.7	7.3 ± 1.0	6.5 ± 0.4	7.1 ± 0.4	7.4 ± 1.1	7.1 ± 0.5
Amphetamine	5	6	5.7 ± 0.8	3.3 ± 0.6	3.4 ± 0.6	3.7 ± 0.9	5.1 ± 0.8	4.7 ± 0.5	5.6 ± 0.6	5.7 ± 0.7
(+)-Amphetamine	2.5	5	6.1 ± 0.7	3.4 ± 0.9	3.8 ± 0.8	5.0 ± 0.8	6.0 ± 0.8	5.4 ± 1.1	6.1 ± 1.0	7.3 ± 1.0
	2.5	5	6.3 ± 0.6	3.4 ± 0.5	4.3 ± 0.5	5.4 ± 0.7	6.2 ± 0.3	5.8 ± 0.6	6.9 ± 0.8	6.9 ± 0.7
	2.5	5	7.2 ± 0.6	4.3 ± 1.0	5.7 ± 0.8	6.4 ± 0.6	6.5 ± 0.7	7.2 ± 1.5	6.6 ± 0.8	7.0 ± 0.7
Fenfluramine	10	6	7.8 ± 0.6	4.0 ± 0.6	7.0 ± 0.5	7.6 ± 0.6	9.0 ± 0.7	9.0 ± 0.8	8.6 ± 0.8	8.6 ± 0.7
Phenmetrazine	25	6	6.6 ± 0.6	4.5 ± 0.5	6.0 ± 0.9	5.9 ± 0.6	6.3 ± 0.7	6.6 ± 0.6	7.3 ± 0.7	7.4 ± 0.7
Diethylpropion	10	6	7.2 ± 0.4	1.4 ± 0.5	2.7 ± 0.9	3.8 ± 1.2	2.8 ± 1.0	4.4 ± 0.8	3.8 ± 0.7	3.7 ± 0.6

Saline or drugs injected subcutaneously daily 30 min before food for 7 days. * Values during the pretreatment week are means of the mean daily values for individual rats pooled over the week.

Table 2 Effect of different anorexigens on first 2 h food intake in fasted rats

Treatment	Dose (mg/kg)	No. of animals	Pre-treatment week*	First 2 h food intake g/100 g body weight (mean ± s.e. mean) Treatment week days						
				1	2	3	4	5	6	7
Control (saline)	—	6	3.1 ± 0.6	4.4 ± 1.0	3.9 ± 0.5	5.3 ± 0.8	4.2 ± 0.4	4.8 ± 0.4	5.2 ± 0.6	4.9 ± 0.4
Amphetamine	5	6	4.1 ± 0.5	0.1 ± 0.07	0.4 ± 0.3	1.2 ± 0.5	1.5 ± 0.4	1.0 ± 0.6	1.2 ± 0.5	1.3 ± 0.4
(+)-Amphetamine	2.5	5	4.4 ± 0.4	1.9 ± 0.6	1.7 ± 0.5	2.1 ± 0.6	2.7 ± 0.2	2.2 ± 1.1	2.2 ± 0.9	2.7 ± 1.2
	2.5	5	4.8 ± 0.4	0.5 ± 0.2	1.2 ± 0.5	1.4 ± 0.5	2.4 ± 0.9	2.7 ± 0.5	3.1 ± 0.3	2.6 ± 0.5
	2.5	5	4.8 ± 0.4	1.6 ± 0.8	2.5 ± 1.0	2.4 ± 0.5	2.5 ± 0.6	3.1 ± 0.7	2.8 ± 0.7	2.8 ± 0.6
Fenfluramine	10	6	5.1 ± 0.5	2.7 ± 0.4	4.8 ± 0.3	4.9 ± 0.3	5.9 ± 0.5	6.2 ± 0.6	6.3 ± 0.6	6.3 ± 0.5
Phenmetrazine	25	6	4.3 ± 0.3	2.2 ± 0.3	3.4 ± 0.4	3.4 ± 0.5	3.6 ± 0.4	3.8 ± 0.5	4.0 ± 0.4	4.1 ± 0.4
Diethylpropion	10	6	5.1 ± 0.4	0.3 ± 0.2	0.7 ± 0.5	1.3 ± 0.7	1.0 ± 0.6	1.0 ± 0.4	1.1 ± 0.5	1.1 ± 0.4

Saline or drugs injected subcutaneously daily 30 min before food for 7 days. * Values during the pretreatment week are means of the mean daily values for individual rats pooled over the week.

taken into consideration for calculation of the dose. The injections were given subcutaneously daily 30 min before food for 7 days. In addition to these, a pair-fed group was maintained in which the rats were allowed to consume the same quantity of food and water daily during the first 2 h period based on the average consumption by the (+)-amphetamine group on the previous day (24 h out of phase). During the second 2 h period they had free access to both food and water, the actual consumption of which was measured daily and recorded. All treatments stopped at the end of one week and the rats were observed for a further period of one (post-treatment) week.

Drugs

The following drugs were used: amphetamine sulphate (E. Merck), (+)-amphetamine sulphate (E. Merck); fenfluramine hydrochloride (Ponderax, Servier); phenmetrazine hydrochloride (Preludin, Boehringer Ingleheim) and diethylpropion hydrochloride (Tenuate, Merrell). The drugs were dissolved in saline and the doses are expressed in terms of the salt.

Statistical analysis

The statistical method employed in the analysis of results was Student's *t* test.

Results

Food intake

The 4 h food intakes following saline, amphetamine, (+)-amphetamine, fenfluramine, phenmetrazine and diethylpropion are shown in Table 1. The mean of the mean daily values for individual rats pooled over the pretreatment week provides the control value for each group. As can be seen, there is an increasing trend in the daily food intake in the saline-treated group. Following fenfluramine and phenmetrazine a similar trend is observed after an initial reduction in the food intake on the first day. However, after amphetamine and (+)-amphetamine intakes during the first three days of treatment were less, after which there was a complete recovery despite the continuation of the treatment. The diethylpropion-treated group showed a marked reduction in the food intake with partial recovery maintained through the rest of the treatment period.

Table 2 shows the first 2 h food intake following different treatments. The saline, fenfluramine- and phenmetrazine-treated groups all showed a similar trend to that seen at the 4 h intake. Amphetamine produced a marked reduction on the first day with a rapid but partial recovery by the third day which was maintained through the rest of the treatment period.

Table 3 Effect of different anorexigens on second 2 h food intake in fasted rats

Treatment	Dose (mg/kg)	No. of animals	Pre-treatment week*	Second 2 h food intake g/100 g body weight (mean ± s.e. mean) Treatment week days						
				1	2	3	4	5	6	7
Control (saline)	—	6	1.2 ± 0.1	1.4 ± 0.6	1.6 ± 0.4	2.0 ± 0.4	2.3 ± 0.4	2.3 ± 0.3	2.2 ± 0.6	2.2 ± 0.5
Amphetamine	5	6	1.6 ± 0.2	3.2 ± 0.6	3.0 ± 0.4	2.5 ± 0.5	3.6 ± 0.5	3.7 ± 0.4	4.4 ± 0.4	4.4 ± 0.4
(+)-Amphetamine	2.5	5	1.7 ± 0.3	1.7 ± 0.4	2.1 ± 0.4	2.9 ± 0.5	3.3 ± 0.6	3.2 ± 0.7	3.9 ± 0.6	4.6 ± 0.6
	2.5	5	1.5 ± 0.2	2.9 ± 0.6	3.1 ± 0.4	4.0 ± 0.4	3.8 ± 0.4	3.1 ± 0.5	3.8 ± 1.0	4.3 ± 0.7
	2.5	5	2.3 ± 0.2	2.6 ± 0.4	3.2 ± 0.4	4.0 ± 0.5	4.0 ± 0.6	4.1 ± 1.1	3.8 ± 0.2	4.2 ± 0.8
Fenfluramine	10	6	2.6 ± 0.2	1.3 ± 0.2	2.2 ± 0.3	2.7 ± 0.4	3.1 ± 0.7	2.8 ± 0.4	2.3 ± 0.2	2.3 ± 0.3
Phenmetrazine	25	6	2.2 ± 0.3	2.3 ± 0.2	2.6 ± 0.6	2.5 ± 0.3	2.7 ± 0.5	2.8 ± 0.5	3.3 ± 0.4	3.3 ± 0.3
Diethylpropion	10	6	2.2 ± 0.2	1.1 ± 0.3	2.0 ± 0.5	2.5 ± 0.6	1.8 ± 0.5	3.4 ± 0.6	2.7 ± 0.5	2.6 ± 0.6

Saline or drugs injected subcutaneously daily 30 min before food for 7 days. * Values during the pretreatment week are means of the mean daily values for individual rats pooled over the week.

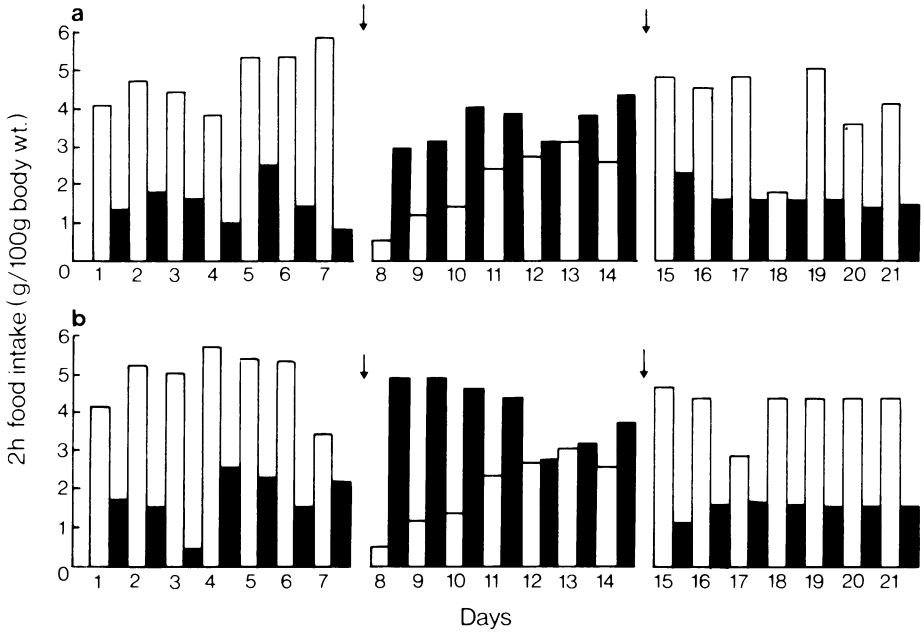

Figure 1 Effect of (a) (+)-amphetamine 2.5 mg/kg; (b) pair-feeding (first 2 h) on 2 h food intake in fasted rats. Open columns—first 2 h period; solid columns—second 2 h period. Drug or saline injected subcutaneously 30 min before food daily between the arrows. Each column represents the mean observations from five rats.

(+)-Amphetamine produced a similar picture except that the reduction was much less than for amphetamine. Diethylpropion had an effect very similar to that of amphetamine.

The second 2 h food intake values are shown in Table 3. After fenfluramine and diethylpropion, a slight reduction on the first day was followed by recovery to almost control level. There was a trend towards a slight increase in the second 2 h food intake following saline as well as phenmetrazine throughout the treatment period. After amphetamine, there was a marked increase in the food intake even on the first day which tended to increase further through the rest of the treatment period. Following (+)-amphetamine, the effect was similar except for some delay in the initial increase of food intake.

The mean first and second 2 h food intake following (+)-amphetamine and in the pair-fed group are

Table 4 Difference in the food intake between the pretreatment and treatment weeks in fasted rats following different anorexigens

			Food intake g/100 g body weight (mean ± s.e. mean)					
			First 2 h			*Second 2 h*		
Treatment	*Dose (mg/kg)*	*No. of animals*	*Pretreatment week*	*Treatment week*	*Difference*	*Pretreatment week*	*Treatment week*	*Difference*
Control (saline)	—	6	3.1 ± 0.6	4.6 ± 0.5	+1.5**	1.2 ± 0.1	2.0 ± 0.3	+0.8*
Amphetamine	5	6	4.1 ± 0.5	1.0 ± 0.3	−3.1***	1.6 ± 0.2	3.6 ± 0.3	+2.0**
(+)-Amphetamine	2.5	5	4.4 ± 0.4	2.3 ± 0.5	−2.1*	1.7 ± 0.3	3.0 ± 0.4	+1.3*
Fenfluramine	10	6	5.1 ± 0.5	4.9 ± 0.2	−0.2	2.6 ± 0.2	2.3 ± 0.1	−0.3
Phenmetrazine	25	6	4.3 ± 0.3	3.3 ± 0.4	−1.0*	2.2 ± 0.3	2.7 ± 0.3	+0.5
Diethylpropion	10	6	5.1 ± 0.4	0.9 ± 0.4	−4.2**	2.2 ± 0.2	2.2 ± 0.4	0
Pair-fed	—	5	—	—	—	1.6 ± 0.1	4.1 ± 0.3	+2.5**

Saline or drugs injected subcutaneously daily 30 min before food for 7 days. Values are means of the mean daily values for individual rats pooled over the respective weeks.
* $P < 0.05$; ** $P < 0.01$; *** $P < 0.001$ (paired t test).

presented in Figure 1. (+)-Amphetamine produced a marked reduction in the first 2 h with only partial recovery, and an absolute increase in the second 2 h food intake during the treatment period. The pair-fed group also showed an increase in the second 2 h food intake, particularly during the first 4 days of treatment which was relatively greater than that after (+)-amphetamine, with a tailing off effect, although the intake remained higher than the pretreatment level. On withdrawal of the treatment the intake returned again to the pretreatment level.

The statistical significance of the changes in food intake are summarized in Table 4. The mean daily intake for each rat was calculated for the pretreatment and treatment weeks and differences analysed for significance by the paired *t* test. During the first 2 h period there was a significant increase in the food intake in the control group but a significant decrease in all the drug-treatment groups except for fenfluramine. During the second 2 h there was a significant increase in all the groups including pair-fed but excluding fenfluramine-, phenmetrazine- and diethylpropion-treated groups.

Water intake

In general, the water intake followed the pattern of food intake with different treatments. There was a significant decrease in the first 2 h water intake after all the drugs including fenfluramine (Table 5). There was also a significant increase in the second 2 h water intake in all the groups except diethylpropion and fenfluramine, the latter producing a significant decrease.

Body weight

The changes in body weight are summarized in Table 6. All the rats lost weight to a varying extent (1.3 to 4.9%) at the end of the pretreatment week. However, the loss at the end of the treatment week was significantly greater after amphetamine, fenfluramine and phenmetrazine. Following (+)-amphetamine there was loss in one series and a gain in two other series during the treatment week, but none of these values was statistically significant. Following diethylpropion, the loss during the treatment week, though apparently greater, was not statistically significant. However, in the pair-fed group there was a significant gain in body weight during the treatment week.

Discussion

The highly potent but short-lived effect (first 2 h) of amphetamines could be explained by the rapid clearance of the drugs as demonstrated by Blundell *et al.* (1975). Similarly the prolonged anorectic effect of fenfluramine (second 2 h) could be explained by the slower rate of clearance of fenfluramine as well as its conversion to another active metabolite, norfenfluramine, reported by the same workers. Complete tolerance to the anorectic effect during the first 2 h food intake was observed after repeated administration of fenfluramine and phenmetrazine, while after amphetamine, (+)-amphetamine and diethylpropion the tolerance was only partial. The monitoring of the daily blood level of these drugs during this period

Table 5 Difference in the water intake between the pretreatment and treatment weeks in fasted rats following different anorexigens

			Water intake ml/100 g body weight (mean ± s.e. mean)					
			First 2 h			*Second 2 h*		
Treatment	*Dose (mg/kg)*	*No. of animals*	*Pretreatment week*	*Treatment week*	*Difference*	*Pretreatment week*	*Treatment week*	*Difference*
Control (saline)	—	6	4.0 ± 0.8	5.5 ± 0.8	+1.5	3.5 ± 0.5	3.5 ± 0.4	0
Amphetamine	5	6	4.5 ± 0.7	0.5 ± 0.3	−4.0**	2.5 ± 0.3	6.0 ± 0.6	+3.5**
(+)-Amphetamine	2.5	5	5.0 ± 0.7	2.5 ± 0.7	−2.5**	2.5 ± 0.6	6.0 ± 0.7	+3.5**
Fenfluramine	10	6	7.5 ± 0.8	5.0 ± 0.4	−2.5*	5.0 ± 0.6	4.0 ± 0.4	−1.0*
Phenmetrazine	25	6	5.5 ± 0.6	2.5 ± 0.7	−3.0**	4.5 ± 0.3	7.0 ± 0.7	+2.5*
Diethylpropion	10	6	6.5 ± 0.5	0.5 ± 0.2	−6.0***	3.0 ± 0.2	4.0 ± 0.7	+1.0
Pair-fed	—	5	—	—	—	2.5 ± 0.2	5.0 ± 0.4	+2.5***

Saline or drugs injected subcutaneously daily 30 min before food for 7 days. Values are means of the mean daily values for individual rats pooled over the respective weeks.
* $P < 0.05$; ** $P < 0.01$; *** $P < 0.001$ (paired *t* test).

might throw some light on the mechanism of the development of tolerance. An absolute increase in the second 2 h food intake presumably contributed towards the development of complete tolerance with respect to amphetamine and (+)-amphetamine when total 4 h food intake was recorded. The pair-feeding experiment suggests that there might be little pharmacological tolerance to amphetamines in the strict sense, but that the anorectic effect is balanced by the increasing deficit of food. It further suggests that there is some carry-over suppressant effect of (+)-amphetamine on the second 2 h intake, specially during the early days of the treatment period.

There was an overall correlation between the food and water intake which was expected because most of the water the rats drink is needed to digest food (Bolles, 1961). Fenfluramine and phenmetrazine, however, had more effect on water than on food intake.

It is interesting that the pair-fed rats gained body weight significantly while the control rats failed to gain any weight. The difference between the two groups was that the percentage loss of body weight during the pretreatment week was less with the pair-fed group. Another difference was that the second 2 h food intake was greater in the pair-fed group than the control group. These differences, however, cannot explain the gain in weight in the pair-fed group and further studies are required to elicit its mechanisms. It should be recognized that rats on a 4-h feeding schedule are to some extent starved and were probably well below normal weight at the start of the treatment week.

The results on body weights following anorexigens are also interesting when compared with their effect on food intake. With the exceptions of (+)-amphetamine and diethylpropion, all drugs produced a significant loss in body weight despite development of tolerance to their anorectic effect. Tormey & Lasagna (1960) observed a similar weight loss following amphetamine despite the development of tolerance. However, diethylpropion is the only drug to which no appreciable tolerance developed and yet it failed to produce significant weight loss. The situation was opposite with fenfluramine. It produced a significant weight loss although its anorectic effect was short lived. It is rather surprising that (+)-amphetamine, affecting food and water intake like amphetamine, failed to produce any significant loss in body weight in starved rats on repeated trials, while amphetamine produced a significant loss. Abdallah & White (1970) also failed to obtain a significant change in body weight in unstarved rats following (+)-amphetamine, while Alphin & Ward (1969), Lawlor, Trivedi & Yelnosky (1969) and Magour, Coper & Faehndrich (1974) reported a loss. The differential effects of (+)- and (±)-amphetamine on body weight in the present series, where the experimental conditions are the same, are opposite to those that would be predicted and are difficult to explain. Body weight is of course the sum of many components which may well vary independently. For instance the effect of amphetamine on body weight could be explained in terms of its adipokinetic action (Opitz, 1970), which is independent of its anorectic effect. Fenfluramine has been shown to increase peripheral glucose utilization (Butterfield & Whichelow, 1968) together with an inhibition of lipogenesis and increase in lipolysis (Marsh & Bizzi, 1972). A significant gain in body weight without any significant change in food or water intake in starved rats has also been reported following

Table 6 Difference in the body weight between the pretreatment and treatment weeks in fasted rats following different anorexigens

Treatment	*Dose (mg/kg)*	*No. of animals*	*Per cent loss of body weight*		
			Pretreatment week	*Treatment week*	*Significance of difference*
Control		6	4.2	4.7	NS
Amphetamine	5	6	4.7	11.8	$P<0.05$
	5	6	4.0	11.8	$P<0.05$
(+)-Amphetamine	2.5	4	3.4	4.3	NS
	2.5	5	2.0	+0.5*	NS
	2.5	5	2.8	+1.9*	NS
Fenfluramine	10	6	3.4	13.8	$P<0.01$
Phenmetrazine	25	6	4.9	15.6	$P<0.01$
Diethylpropion	10	6	2.3	9.1	NS
Pair-fed	—	5	1.3	+3.8*	$P<0.01$

Drugs injected subcutaneously daily 30 min before food for 7 days. Values represent the difference between first and seventh day body weight expressed as per cent of the first day weight in the week. * Represents gain in body weight.
Significance of difference between the two weeks by Student's paired *t* test.

cyproheptadine (Ghosh & Parvathy, 1973a). The effect of a drug on metabolism rather than, or in addition to, its effect on food and water intake may be a factor in explaining the mechanism of the alteration of body weight.

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