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Tolerance to Anorectic Drugs: Pharmacological or Artifactual[1]

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LEVITSKY, D. A., B. J. STRUPP AND J. LUPOLI. *Tolerance to anorectic drugs: Pharmacological or artifactual.* PHARMAC. BIOCHEM. BEHAV. **14**(5) 661–667, 1981.—The results of three studies are presented which demonstrate that the anorexia produced by amphetamine and fenfluramine is secondary to a direct weight suppressing effect of these drugs. Furthermore, these data strongly suggest that the decreasing weight loss and the return to normal appetite that occurs with repeated drug usage is not due to pharmacological tolerance, but rather reflects a successful physiological and behavioral adjustment to a lowered level of body weight.

Anorectic drugs Tolerance Body weight regulation Food intake Appetite

AMPHETAMINE has long been used in the treatment of obesity, due to its effectiveness in suppressing appetite [11,20]. However, there are several properties of this drug that make its use in therapy less than ideal. One of the major deleterious properties is the development of tolerance. Tolerance, as classically defined, is the decrease in the effectiveness of a drug with repeated administration [12]. Tolerance to the anorectic effects of amphetamines has been repeatedly observed in both animals [18] and humans [1]. What is unusual about the tolerance to amphetamines is that it seems to be limited to the anorexia, since other behavioral effects of the drug such as increased motor activity and stereotypy [18] do not show tolerance with repeated administrations.

The traditional explanation of drug tolerance is based on a decrease in the sensitivity of drug receptors (pharmacodynamic tolerance) or an increase in the effectiveness of the drug degrading systems (drug disposition tolerance). However, an alternative explanation of the tolerance to anorectic drugs is also possible. One consequence of an administration of an anorectic drug is a loss in body weight. It is possible that the effectiveness of the anorectic drug is directly related to level of body weight. Thus, what appears as the development of tolerance with repeated administration of the drug may, in fact, be the result of the accompanying decline in body weight. The studies reported below explore this latter explanation of the development of tolerance to two commonly used anorectic drugs, amphetamine and fenfluramine.

EXPERIMENT 1: EFFECT OF PRIOR WEIGHT LOSS ON AMPHETAMINE-INDUCED ANOREXIA

If the weight loss hypothesis of tolerance is correct, then the anorectic effectiveness of amphetamine should be greatly diminished by reducing body weight prior to drug administration.

METHOD

Thirty-nine albino female rats were divided into four groups matched on the basis of body weight and daily food intake. Both the control group (C) (n=9) and the weight reduced (RC) nondrugged group (n=10) received 1 cc of tap water daily, administered through stomach gavage, from day 1 to day 60 of the experiment. Two groups, the drugged (D) (n=10) and weight reduced drugged (RD) (n=10) group, received 1 cc of water via stomach gavage from day 1 until day 6, then were given 30 mg/kg of d-amphetamine sulfate from day 7 until day 60. The dosage was calculated according to body weight on day 1 and was held constant throughout the experiment. The weight reduced groups were deprived of food during the first 6 days of the experiment; thereafter they received free access to ground Agway rat chow in their home cages. Food intake was calculated daily for each animal to the nearest tenth gram, and was equal to the difference between the starting weight of the food cup plus chow and the ending weight, minus the spillage. All animals were housed singly, had continual access to water, and were maintained on a 12-hour light-dark cycle. Room temperature was held constant at 25°C.

RESULTS AND DISCUSSION

The results of these manipulations on food intake and body weight can be seen in Fig. 1. The conventionally drug treated animals which received the drug at their normal body weight showed the typical tolerance pattern. When drug treatment began there was a statistically significant suppression in daily food intake of D group compared to RD group

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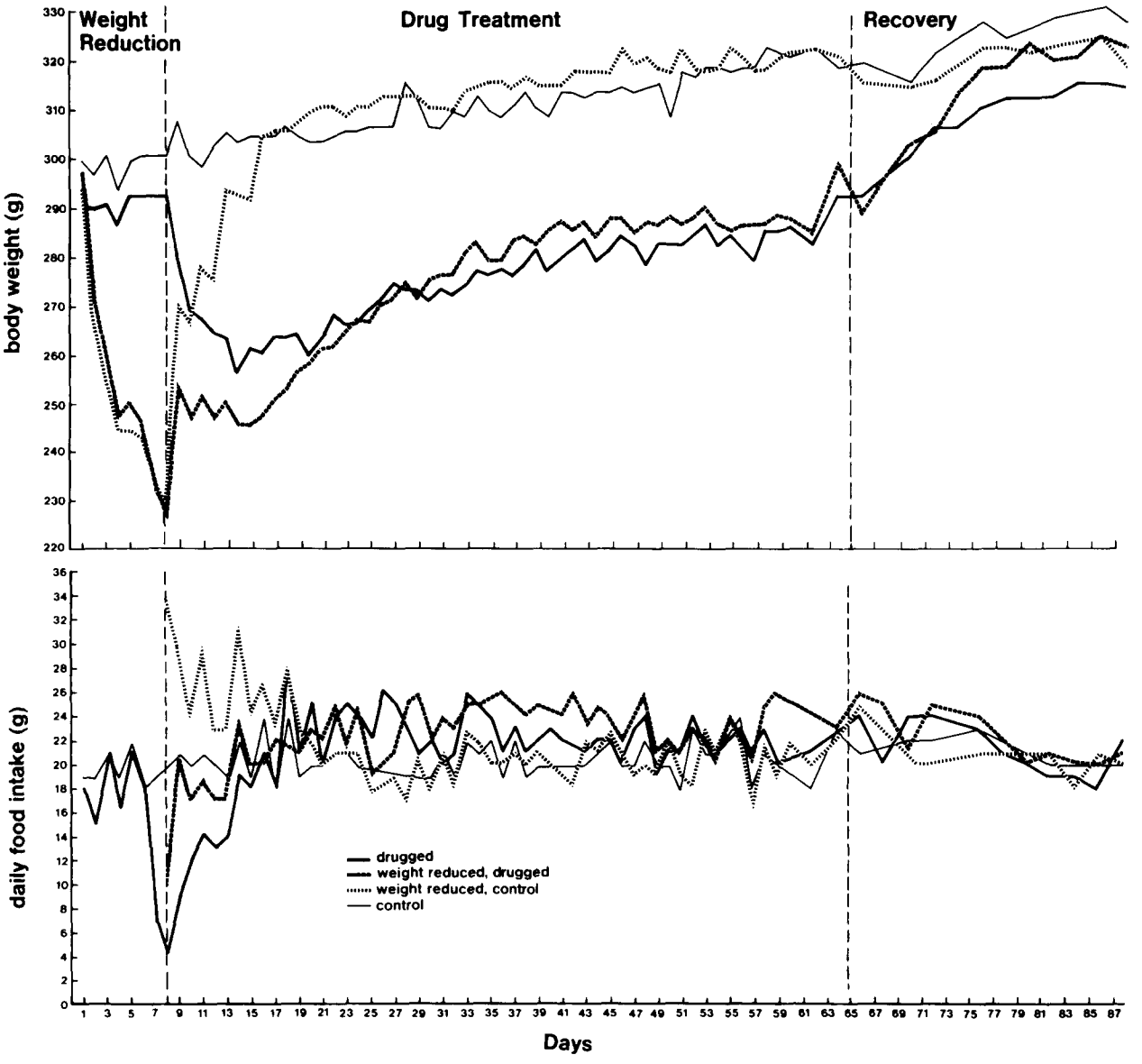

FIG. 1. Mean daily food intake and body weight. Drugged groups received amphetamine daily for duration of drug treatment.

($t=6.23$, $p<0.001$), which gradually diminished by the fourth day of drug treatment. Body weight decreased sharply during this period and plateaued to a value which remained parallel to, but significantly less than, the control group ($t=4.71$, $p<0.001$).

The groups that were food-restricted on days 1 through 6 lost approximately 65 grams of body weight. Unlike the conventionally treated amphetamine group (D), the previously restricted group (RD) displayed no signs of amphetamine-induced anorexia. This result is particularly striking in view of the extremely high drug dosage used. Body weight actually increased during the first several days of drug administration, and reached the same asymptotic value as did the conventionally-treated drug group. The non-drugged group (RC) that was food-restricted during the first six days of the experiment displayed the typical postfast hyperphagia for approximately four days. Body weight of this group returned to the same level as did the control group.

The suppression of body weight of the amphetamine-treated groups was clearly drug dependent since the cessation of amphetamine administration (during recovery) caused an increase in body weight, reaching the level of the nondrugged groups in approximately one week. It is interesting to note that this recovery of body weight was accomplished without an increase in food intake.

These results demonstrate that the anorectic effect of amphetamine is greatly influenced by prior body weight loss. Establishing a loss in body weight prior to amphetamine administration clearly counteracts the anorexia. Since diet-induced weight loss lessens the amphetamine-induced

anorexia, it seems reasonable that the weight loss that results from repeated amphetamine administrations also counteracts the anorectic effectiveness of the drug. The result of this antagonism between weight loss and drug-induced anorexia, then, appears as tolerance in those situations in which body weight does not completely recover between successive drug administrations.

It is important to point out that the suppression of body weight that was observed during drug treatment was maintained despite the fact that daily food intake returned to control levels. This sustained depression in body weight is not the result of the initial anorexia. We have shown elsewhere that rats will completely recover body weight following fasting when permitted to consume no more than normal daily food intake [17]. Moreover, the recovery of body weight occurred immediately following cessation of drug treatment. These facts suggest, therefore, that the amphetamine-induced weight loss may not be due solely to a depression in food intake, but also may be the result of an increase in energy expenditure.

EXPERIMENT 2: EFFECT OF PRIOR WEIGHT LOSS ON FENFLURAMINE-INDUCED ANOREXIA

Another widely used anorectic drug, fenfluramine, while structurally similar to amphetamine, apparently acts through different neurotransmitter and behavioral systems [4, 5, 29]. However, as in the case of amphetamine, animals [14] develop an apparent tolerance to the anorectic effects of fenfluramine, although little tolerance seems to develop to other behavioral effects of the drug [29]. In order to determine the generality of our conclusions concerning the nature of tolerance to anorectic drugs, the following studies were performed with fenfluramine.

METHOD

Basically the experimental design of the first experiment was used in the second study, with one major difference in procedure. In the first experiment, a rather high dose of amphetamine was administered daily. This was necessary in order to prevent the animals from recovering their body weight within 24 hours. In the second study, we restricted the animals' food access to six hours each day. This permitted us to use a smaller drug dosage while still inducing a sustained loss in body weight over a 24 hour period.

Twenty-three female albino rats were trained to consume all their ration within six hours. For the first six days of the study all animals received 1 cc of tap water daily via stomach gavage, one-half hour before the six hour feeding session. The control group, group C (n=5), and the weight reduced nondrugged group, RC (n=6) continued to receive tap water throughout the study. From day 7 until day 27, groups D (n=6) and RD (n=6) were intubated with 20 mg/kg fenfluramine hydrochloride dissolved in 1 cc tap water. The dose was calculated on the basis of the body weight of each animal on day 1 and was held constant throughout the remainder of the study. Intake of groups RC and RD was limited to 5 grams of food daily for the first 5 days of the experiment, and increased to 7 grams on day 6. Thereafter all animals had unlimited access to food during the 6 hour feeding period. Water was always available. Animals were housed in individual cages and were maintained under a 12-hour light cycle, with all manipulations occurring during the 12 hours of darkness.

RESULTS AND DISCUSSION

The results, as shown in Fig. 2, are almost identical to those found in the amphetamine study. Group D displayed the typical tolerance pattern; food intake was initially depressed by fenfluramine treatment ($t=7.19$, $p<0.001$), and body weight declined. After 6 days, food intake returned to nondrug values, but body weight remained significantly depressed ($t=3.02, p<0.025$) for the duration of drug treatment. Animals in group RD, on the other hand, that were first reduced in body weight, showed no anorexia when compared to the control group (C), and actually gained weight until their weights reached the level of the other fenfluramine treated group (D). As in Experiment 1, mean body weight of group RD remained parallel to that of the control group until the termination of drug treatment, when it increased to the level of the nondrugged groups. Group RC showed normal recovery following the period of food restriction, displaying a short period of hyperphagia with a complete recovery of body weight to the level of the nonrestricted group.

The results of this study demonstrate that fenfluramine, like amphetamine, produces anorexia which is antagonized by body weight loss. The typical fenfluramine anorexia was blocked by reducing body weight prior to drug administration. Also, as in the case of amphetamine, body weight was continually suppressed by fenfluramine, even though food intake rapidly returned to normal levels. Thus, even though amphetamine and fenfluramine appear to act through different brain mechanisms, both drugs seem to have a direct suppressing effect upon body weight. Furthermore, the anorectic effect of these two drugs appears to diminish as body weight decreases, and thus resembles the phenomenon of tolerance.

EXPERIMENT 3: REESTABLISHING ANOREXIA IN "TOLERANT" ANIMALS

If the weight loss interpretation of tolerance is correct, then it should be possible to reestablish the anorectic effect of the drug in fenfluramine-"tolerant" animals by experimentally raising body weight to predrug values. The purpose of the final study in this series was to directly test this prediction.

METHOD

Three groups of female albino rats were intubated daily with 20 mg/kg fenfluramine hydrochloride one-half hour before the 6 hour feeding period. A control group, C (n=5), received 1 cc of tap water daily. Beginning on day 41, all animals were intubated daily with a 10 cc gastric load two hours following the end of the six hour feeding period. Two of the forced-fed groups, FD (n=7) and FDC (n=6), were intubated with 25 calories of a liquid diet. The liquid diet used was a solution composed of 16 calories dry tube feeding diet (supplied by GBC) and 9 calories vegetable oil. Group D (n=5) and the control group (C) were intubated with 10 cc of tap water. Starting on day 55, additional daily stomach loading was performed 7 hours following the end of the feeding period; thus the forced-fed groups then received a total daily intubation of 50 calories. On day 65, all gastric feeding was terminated. Daily fenfluramine administration was terminated on day 64 for group FDC.

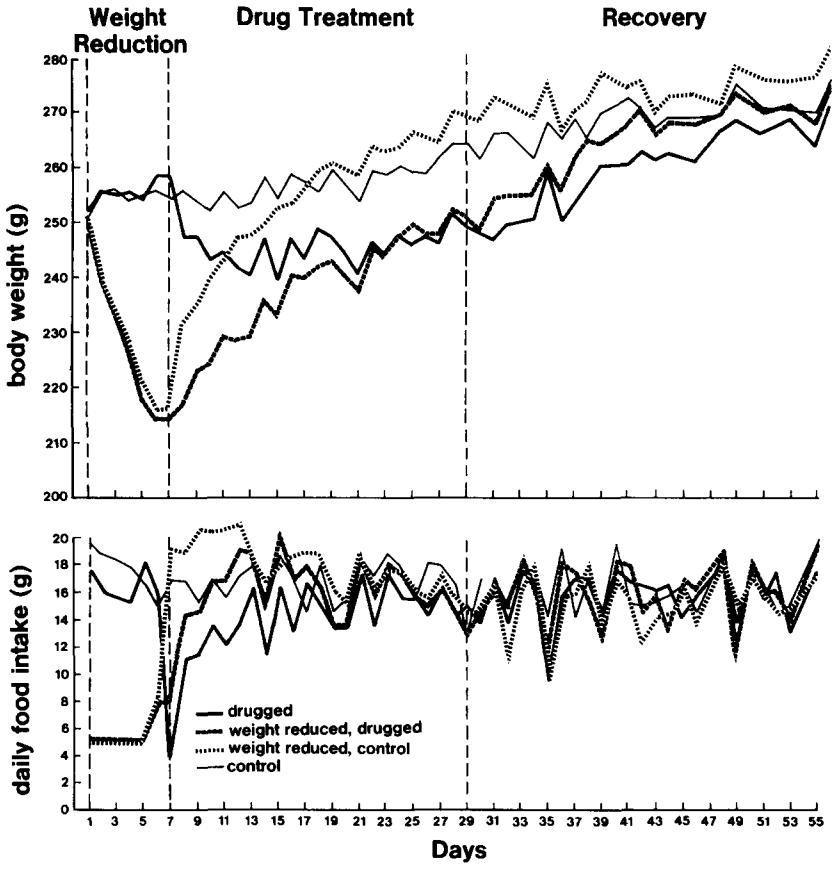

FIG. 2. Mean daily food intake and body weight. Drugged group received fenfluramine daily for duration of drug treatment.

RESULTS AND DISCUSSION

The results of this study are presented in Fig. 3. Fenfluramine treatment of animals at normal body weight produced an immediate suppression in food intake ($t=8.40$, $p<0.001$) which gradually disappeared in about a week. Body weight, similarly, showed an immediate decline resulting in a significant depression ($t=4.80$, $p<0.001$). This drug-induced suppression of body weight remained throughout the entire 91 days of the study. The change in body weight of the control group (C), from day 8 until day 92 was not significantly different from that of the chronically-treated fenfluramine group (D) for the same period.

Forced feeding produced a depression in food intake and an increase in body weight. By the end of the forced feeding period the mean body weight of both groups of forced-fed animals, groups RD and FDC, was significantly elevated above that of the control group ($t=3.29$, $p<0.005$).

On the first day after forced feeding began, daily food intake declined. This decline was not due to stomach fill, since intubations occurred at least 12 hours prior to feeding, a period of time sufficient to allow gastric emptying. Moreover, the suppression in food intake continued for about a week after forced feeding had been terminated. More likely, the inhibition of food intake was related to the gain in body weight that resulted from the excessive caloric intake. This suppression of food intake as a result of forced feeding and weight gain has been commonly observed by others [7]. What is particularly important is that the anorexia began when body weight rose above the drug-induced level, a level significantly below nondrugged body weight.

The fact that the anorectic effectiveness of fenfluramine was reestablished by forced feeding is demonstrated by a comparison of food intakes of the two forced-fed groups. When the fenfluramine treatment was terminated for the forced-fed group (FDC), their mean food intake increased significantly above that of the forced-fed, but drug maintained group (FD). Food intake for the FD group was 0.8 g (± 0.42), whereas the main food intake for the FDC group was 3.1 g (± 0.38), the difference being statistically significant ($t=6.43$, $p<0.001$).

Further evidence that the anorectic effect of fenfluramine could be re-established in supposedly "tolerant animals" can be drawn through a comparison of the length of time that the anorexia remained in the two forced-fed groups. Recovery of normal food intake was defined for each animal as the day on which daily food intake was not statistically different from subsequent daily intakes. Animals that were taken off the drug following forced feeding (group FDC) recovered their normal daily food intake in 6.5 ± 1.2 days. The rats that continued on the drug following cessation of forced

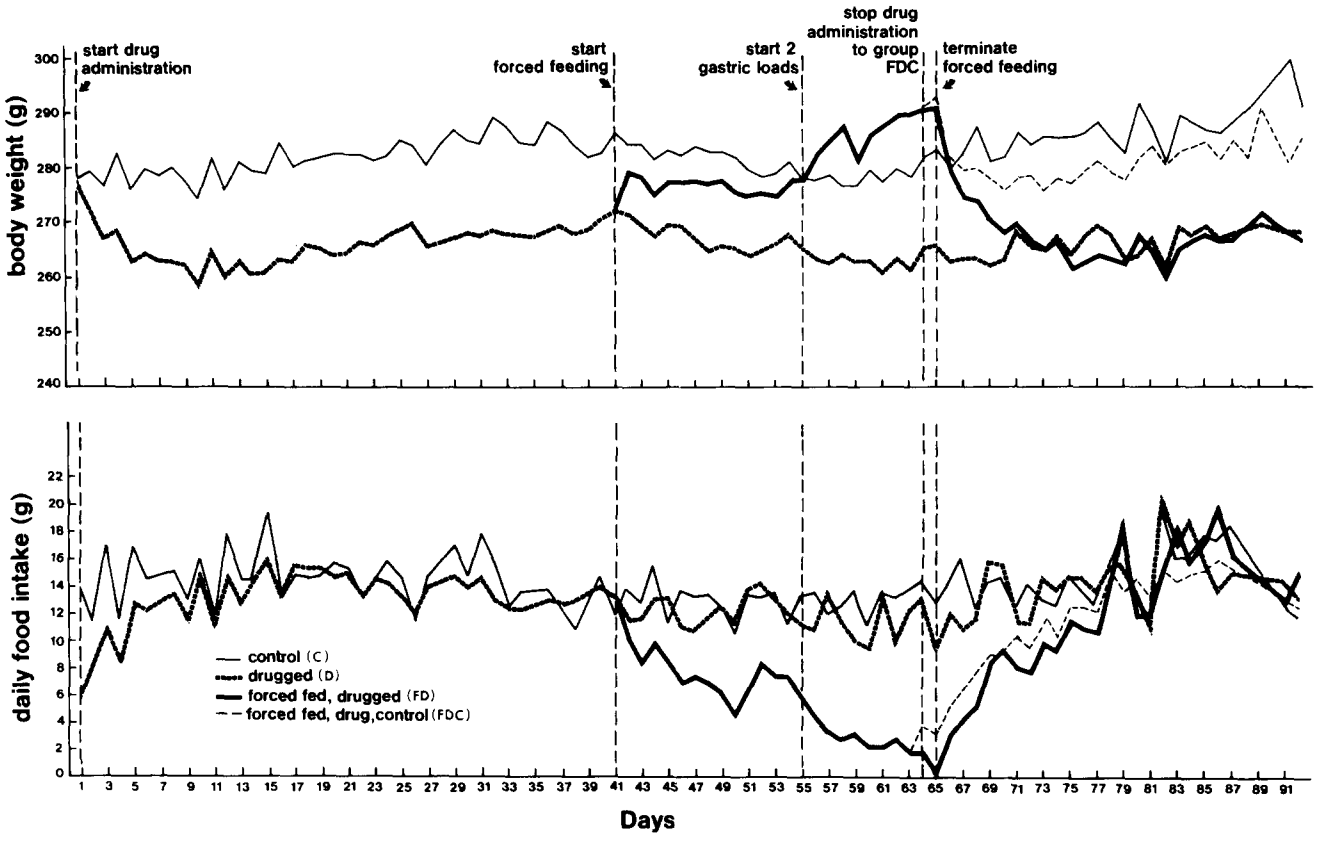

FIG. 3. Mean daily food intake and body weight. Drugged groups received fenfluramine daily. Forced feeding consisted of a gastric load of 10 cc of a liquid diet inserted via stomach tube.

feeding (group FD) required 9.9±2.9 days to return to normal daily food intake. The difference in recovery time between the two groups was statistically significant ($t=2.78$, $p<0.025$).

GENERAL DISCUSSION

The results of these studies strongly support a weight loss explanation of the tolerance to anorexic drugs. These data show quite clearly that the effectiveness of amphetamine and fenfluramine in producing anorexia is decreased by a reduction in body weight. What appears to be pharmacological tolerance to the anorectic effects of chronic drug administration is merely a reflection of decreasing body weight. In light of these data, an explanation of tolerance to the anorectic effects of fenfluramine and amphetamine that is based on pharmacological mechanisms seems quite untenable, a conclusion also reached by Carlton and Wolgin [6], Panksepp and Booth [22], and Ghosh and Parvathy [10].

Carlton and Wolgin injected one group of deprived rats with amphetamine prior to a limited period of access to a preferred food, with an injection of saline following the "meal." A second group of rats received the same two injections but in the reverse order. The first group of animals developed tolerance to the anorexic effects of the drug, while, over the same period of time, the second group did not. The authors conclude that "the development of tolerance is contingent on the relationship between time of injection of amphetamine and eating." However, the weight loss hypothesis of tolerance can also explain the findings of Carlton and Wolgin, as well as several aspects of the data in the present study which the "contingent tolerance" theory is unable to account for. The weight loss hypothesis would predict that those animals who were losing weight as a result of daily amphetamine administration (as was surely the case for the animals receiving pre-meal injections) would become tolerant to the anorexic effects of the drug, while those who were able to maintain a constant body weight (the post-meal amphetamine group) should not develop tolerance. The results of Carlton and Wolgin's study are consistent with this view.

The contingent tolerance theory, however, cannot account for several aspects of the present data; it cannot explain either the absence of anorexia when body weight is reduced prior to the initial administration of amphetamine (Experiment 1), or the re-establishment of anorexia after "tolerance" has already developed (Experiment 3).

Another alternative explanation to a strict pharmacological interpretation to the tolerance which develops to anorexic drugs is put forth by Panksepp and Booth [22]. In this study, one group of rats was fed chow adulterated with amphetamine, and a second group of rats was pair-fed with regular chow. After several days, the "yoked" group was also fed adulterated chow. These yoked animals ate signifi-

cantly more adulterated chow on the first day, and equivalent amounts on the subsequent four days. The authors conclude from these data that the tolerance seen with chronic amphetamine administration is due to accruing food deprivation, an explanation also advocated by Ghosh and Parvathy [10]. However, the yoked animals were surely at a reduced weight at the time they received the first administration of the drug. Thus, the attenuation of anorexia seen in these animals can also be explained by the weight loss interpretation of tolerance.

Although the theory of accruing food deprivation can explain the absence of anorexia observed when body weight is reduced prior to the initial drug administration (Experiments 1 and 2), the theory has several weaknesses which limit its usefulness as a cogent explanation for the tolerance-like effect of anorectic drugs. First, it is very clear from all the experiments described above that daily food intake of animals chronically receiving an anorectic drug asymptotes at normal control values. The theory of accruing food deprivation would predict that food intake should plateau at a value less than control values. This prediction is based on the fundamental conception that the level of food intake is the resultant of two forces: one force is generated by the accruing food deprivation, which tends to increase food intake. The opposing force is that produced by the pharmacological action of the drug which depresses food intake, an effect which Panksepp and Booth argue is immune from pharmacological tolerance.

The other weakness in the accruing food deprivation hypothesis is that it cannot account for the re-establishment of the anorexia observed in Experiment 3.

It is particularly important to note that although the effect of amphetamine and fenfluramine on food intake was transitory, there was no indication from any of these studies that tolerance developed to the weight suppressing effect of these drugs. This point was made especially clear by the results of the third study in which the body weight of one of the groups (D) was maintained on daily fenfluramine treatment for nearly 80 days and did not show any evidence that this effect of the drug was diminishing.

One possible explanation for both the "apparent" tolerance phenomenon and the continued suppression of body weight with the chronic use of amphetamine and fenfluramine is based on the thermogenic effect of these drugs. Although amphetamine and fenfluramine produce differential effects on body temperature [3,13], both drugs increase heat production [21]. However, a tolerance seems to develop to the thermogenic effect when the drugs are administered daily [21]. It is possible that the thermogenic effect, like the anorectic effect, is depressed by the weight loss which accompanies chronic administration of the drug. Since agents that increase heat production in thermoneutral environments such as epinephrine [26], glucagon [28], prostaglandin [2], exercise [16], anxiety [25,27], and pyrogens [15], also cause anorexia, it is not unreasonable to suggest that the initial anorexic effect of fenfluramine and amphetamine may result, at least in part, from the enhanced heat production. The suppression in food intake would disappear as the thermogenic effect of repeated drug administration decreases with the loss in body weight.

It is also likely that the metabolic effect of these drugs does not completely disappear. This effect is strongly suggested by the observations cited in the results, that chronic amphetamine and fenfluramine use produces a sustained depression in body weight while food intake clearly returns to normal levels. There exists abundant evidence demonstrating that agents which increase metabolic rate, such as cold [24], exercise [23], glucagon [9], epinephrine [8], thyroxine [19], and estrogens [30], also depress body weight (particularly fat content) in mammals.

We suggest that the effect of the initial administration of an anorectic drug is to produce an increase in heat production that inhibits food intake, thus directly and indirectly causing a loss in body weight. The thermogenic effect of repeated aministration of these drugs decreases with the loss in body weight which, in turn, releases the inhibition on feeding behavior. The drug-induced increase in metabolic rate does not completely disappear, and may be responsible for the continued suppression of body weight, an effect to which tolerance does not develop.

In summary, the research described above demonstrates that what appears as tolerance to the anorectic effects of chronic amphetamine and fenfluramine treatment does not represent pharmacological tolerance, but rather a decrease in drug-induced anorexia due to a reduced body weight. It is postulated that part of the anorectic action of these drugs as well as the continued depression in body weight may be due to the thermogenic action of these drugs.

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