Food Deprivation Increases Oral and Intravenous Drug Intake in Rats

Abstract. *Rats given continuous access to etonitazene hydrochloride in their drinking water (5 micrograms per milliliter) more than doubled their drug intake while deprived of food. Another group of rats with implanted jugular catheters self-administered etonitazene (10 micrograms per kilogram) intravenously on a continuous reinforcement schedule, and the number of infusions increased significantly on days when they were deprived of food. These results suggest that feeding condition may be a powerful determinant of drug-reinforced behavior.*

Food deprivation has a variety of effects on liquid intake and feeding-related behaviors in rats. For instance, it is known that food deprivation is accompanied by decreases in water intake (*1*, *2*). However, other drinking behaviors have been reported to increase with food deprivation: consumption of saccharin solutions (*3*) and water drinking produced by injections of hypertonic saline (*2*) or after hypothalamic lesions (*4*). Intracranial self-stimulation (*5*) and mouse killing (*6*) also increase during food deprivation.

Methods developed to induce oral drug intake in laboratory animals [for example, see (*7*)] often require food deprivation. However, the effects of food deprivation on drug intake have not been studied, especially regarding drugs other than ethanol. Previous reports have shown that food deprivation increases oral ethanol intake in rats having access to the drug 1 or 6 hours daily by lever-pressing in operant chambers (*8*).

In the research reported here we investigated the effects of food deprivation on the intake of etonitazene-HCl (National Institute on Drug Abuse, Research Triangle Institute). Etonitazene is an opioid approximately 1000 times as potent as morphine, noncaloric, and apparently low in aversive taste properties (*9*). In the first experiment, rats were given continuous access to the drug in their drinking water. In the second experiment, another group of rats were given continuous intravenous access to etonitazene through an implanted jugular catheter to minimize the contribution of taste factors.

In the first experiment, 34 adult male albino Wistar rats (360 to 380 g) were divided into four groups. The experimental treatments were arranged such that each group had conditions of unlimited access to etonitazene (E) or water (W), and either food deprivation (FD) or food satiation (FS). The four groups were labeled according to treatment: E-FD (N = 9), E-FS (N = 8), W-FD (N = 9), and W-FS (N = 8). Body weights, food, and liquid intake were measured for each rat between 7:30 and 9:00 a.m. each day. The rats were housed in individual stainless steel wire-mesh cages (Hoeltge) throughout the experiment. Drinking solutions were available in 250-ml bottles with stainless steel drinking tubes attached to the front of the cages. The bottles were weighed, cleaned, and replaced with fresh solutions every 24 hours and corrections (0.5 ml) were made for spillage.

The experiment was divided into four phases. During phase 1 (5 days) a water intake baseline was obtained for all rats. Each group had free access to tap water and 40 g of food pellets (Noyes standard 45 mg) each day. During phase 2 (5 days) an etonitazene intake baseline was obtained; groups E-FD and E-FS were allowed continuous access to etonitazene (5 μg/ml) and groups W-FD and W-FS continued to receive water freely. In phase 3 (23 days) groups E-FD and W-FD were reduced to 75 percent of their mean body weights as determined during phase 2. This was accomplished by feeding the rats 8 g of food per day until the 75 percent weight was reached, then an amount necessary (12 to 14 g) to maintain that weight for 5 days. Rats in groups E-FS and W-FS continued to receive 40 g of food per day. Phase 4 was identical to phase 2, with all rats receiving 40 g of food per day. Actual food intake never exceeded 36 g.

While food-satiated during phases 1 and 2, all four groups drank similar volumes of water and etonitazene (Fig. 1). However, food deprivation during phase 3 resulted in substantial differences among the four groups. The etonitazene-food-deprived group (E-FD) nearly doubled their intake of the etonitazene solution (5.0 μg/ml), while the etonitazene-food-satiated group (E-FS) increased their drug intake only slightly. In contrast, the water-food-deprived group (W-FD) decreased their water intake by one-half, and the water-food-satiated group (W-FS) showed no change in water intake. These changes slowly returned to baseline conditions during phase 4, when all groups were again food-satiated. During phase 3 the E-FD group increased their daily drug intake from 0.4 to 1.12 mg/kg, while the drug intake of the E-FS group increased only from 0.45 to 0.49 mg/kg.

The daily fluid intake of individual rats in group E-FD during phase 3 ranged from 30 to 250 ml and consistently fluctuated from high to low on alternate days, with each rat showing this alternating pattern. The liquid intake for individual rats in the other three groups did not vary more than 10 ml on any two successive days. The standard error (S.E.) of daily intakes ranged from 0.9 to 5.8 for groups E-FS, W-FS, and W-FD throughout all four phases of the experiment. The daily S.E.'s for group E-FD were within this range for phases 1 and 2; however, they increased from 4.0 to 15.3 during phase 3, then decreased from 13.4 to 3.9 during the first 5 days of phase 4. The E-FD group demonstrated stereotyped behaviors similar to those previously reported to accompany etonitazene (*10*) and morphine (*11*) intake. The stereotypy was predominantly characterized by repetitive biting of the front paws; it became worse on days of high drug intake. However, self-mutilation and other stereotyped behavior ceased abruptly when the rats were food-satiated, and this behavior did not occur in any of the other groups.

The large drug intake and daily variability of group E-FD appeared to be specific to the interaction between etonitazene intake and food deprivation. Food deprivation alone (in group W-FD) resulted in a decrease in liquid intake. The increased levels of drug intake in group E-FD are not explained by tolerance alone, as the food-satiated group (E-FS) increased their etonitazene consumption by only a small amount over the same period. Furthermore, the increase in etonitazene intake in both food-deprived and food-satiated groups was not a result of increased hydrational needs in young adult rats, as the water intake of group W-FS showed no steadily increasing trend.

Although it appears that food deprivation was a necessary condition to produce large volume intakes of etonitazene, this condition alone did not produce self-mutilation and stereotypy, as these behaviors were not observed in group W-FD. It appears from these results that the combination of food deprivation and etonitazene intake was responsible for the stereotyped behaviors; however, this conclusion indicates that further control procedures are warranted. For instance, it is possible that food-satiated rats induced to consume quantities of etonitazene similar to those consumed by group E-FD, by taste adul-

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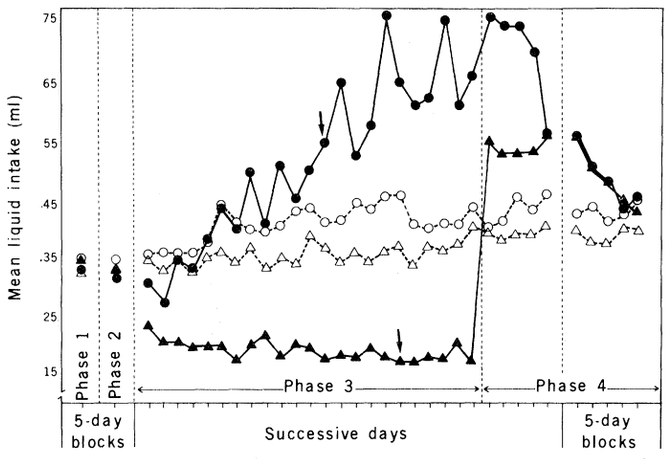

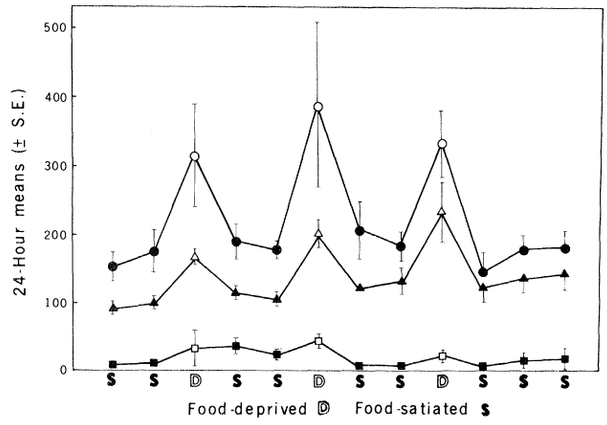

Fig. 1 (left). Mean liquid intakes for the four groups, (●) E-FD, (○) E-FS, (▲) W-FD, and (△) W-FS, for the four experimental phases (panels 1 to 5). Data for phases 1 and 2 and part of phase 4 (panels 1, 2, and 5) are presented in blocks of 5-day means. Daily group means are presented for phase 3 (panel 3) and the first 5 days of phase 4 (panel 4). Arrows indicate the day when all animals in the food-deprived groups had reached 75 percent of their body weight. Fig. 2 (right). Mean (± standard error) numbers of (circles) drug-lever responses, (triangles) etonitazene (10 μg/kg) infusions, and (squares) activity responses for consecutive food-satiation (closed symbols) and food-deprivation (open symbols) days. Each point represents a mean for five rats.

teration of the drug solution or by parenteral means, would show similar behaviors.

The second experiment was conducted to determine whether the increase in drug intake as a result of food deprivation would also occur with the intravenous route of self-administration. Five naïve male Wistar rats (375 to 400 g) were implanted with intravenous jugular catheters by methods similar to those described by others [for example, see (*12*)]. After 2 or 3 days of recovery in the home cages, the rats were each housed in an operant chamber containing a "drug" lever and an "activity" lever. Each response on the drug lever produced an infusion of etonitazene (10 μg/kg) lasting approximately 10 seconds. Responses on the other lever had no effect and were used as a measure of nonspecific activity.

The rats were allowed unlimited access to etonitazene on a continuous reinforcement schedule; that is, each lever press produced an infusion. All five rats began to self-administer etonitazene after only a few hours in the chamber, but the first day of data collection followed an initial 24-hour adaptation period. They had unlimited access to food, except on every third day, when they were given only 8 g of food. Water was continuously available on all days. This food satiation and deprivation sequence was repeated three times, ending with 3 days of food satiation.

Figure 2 shows a clear increase in drug responding and infusions on days of food deprivation. Responses were often made during infusions; thus, the number of responses is consistently greater than the number of infusions. Separate means for responses, infusions, and activity responses were obtained for each rat on the three food-deprivation days, and the three food-satiation days immediately preceding the food-deprivation days. Repeated measures t-tests comparing these means revealed that drug responses and infusions for the five rats were significantly higher on food-deprivation days ($t = 2.59$, d.f. $= 4$, $P < .05$ and $t = 6.88$, d.f. $= 4$, $P < .05$, respectively); however, the mean activity responses were not significantly different under conditions of food deprivation or satiation ($t = 2.05$, d.f. $= 4$, $P > .05$). The relatively constant behavior during the final three food-satiation days suggests that the increases in responses and infusions were due to food deprivation rather than a nonspecific pattern of drug self-administration.

The rate of drug intake on food-satiation days was relatively constant at approximately four infusions per hour or approximately 1 mg/kg-day. The pattern on food-deprivation days was identical to that on food-satiation days for the first 8 hours; however, after the first 8 hours, the infusion rate rapidly increased to approximately eight infusions per hour and remained constant at that level throughout the remaining 16 hours. The average rate of etonitazene intake on food-deprivation days was approximately 1.9 mg/kg-day. No stereotypy or self-mutilation was noted in these rats; however, they were ataxic and often appeared highly intoxicated.

The results of the first experiment showed that food deprivation increased oral etonitazene intake and decreased water intake. The second experiment demonstrated that the increased drug intake is not limited to the oral route of self-administration. Thus, it is not likely that the increases in oral drug intake during food deprivation are due to increased palatability of the drug solution.

The results of the oral etonitazene experiment agree with earlier findings from this laboratory concerning increases in ethanol intake in rats during partial food deprivation (*8*). Increases in ethanol intake could be interpreted as caloric replacement, but this explanation would not apply to the etonitazene experiments. The results of the intravenous etonitazene experiment have recently been replicated in similar experiments with other groups of naïve rats self-administering infusions of cocaine (0.1 mg/kg) (*13*) and phencyclidine (0.125 mg/kg) (*14*). Others have noted that rates of schedule-induced self-injection of nicotine and *d*-amphetamine are higher in rats that are maintained at reduced body weights (*15*). Thus, the food deprivation effect occurs with drugs from the four major classes of drugs abused by humans.

The increasing generality of this finding argues against interpretations involving specific actions of a major class of drugs such as anorexia, the central nervous system depressant action of the general depressants and the opioids, or a specific role of the endorphins. Instead, the agreement across drug classes suggests a more general interpretation, such as a learning mechanism whereby the interoceptive stimuli related to partial food deprivation become associated with the reinforcing properties of the drugs.

Evidence from the present study supports a learning interpretation. In the intravenous experiment, the mean number of infusions increased by about 30 on each successive food-deprivation day, and this effect was even more pronounced (more than 100) in a subsequent replication of this experiment with cocaine (*13*). These increases are not explained by tolerance since there were no increasing trends in infusions (for either drug) on food-satiation days. Thus, the increase in drug intake on food-deprivation days may have been a result of the repeated pairing of food deprivation with the reinforcing effects of the drugs. There are also data from an extension (*16*) of the present oral etonitazene experiment showing more rapid increases in etonitazene intake as a result of repeated exposures to food deprivation and etonitazene access. At the end of phase 4, group E-FD was deprived of food a second time. Mean etonitazene intake increased to previous food deprivation levels within 1 or 2 days. By contrast, in phase 3 it initially took 17 days for etonitazene intake to reach maximum levels and stabilize.

Food deprivation is routinely used in many areas of behavioral research, including animal tests employed in the initial screening of psychoactive drugs to classify them and to evaluate their abuse liability. An implication of the present research is that food deprivation, and possibly other deprivational states, may have a substantial effect on the outcome of preclinical drug research, and this variable should be controlled in the design of such experiments. In more general terms, feeding condition or deprivational state appears to represent a major class of variables controlling drug-reinforced behavior in laboratory animals.

MARILYN E. CARROLL
CHARLES P. FRANCE
RICHARD A. MEISCH

Psychiatry Research Unit, University of Minnesota, Minneapolis 55455

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Sucrose Consumption Early in Life Fails to Modify the Appetite of Adult Rats for Sweet Foods

Abstract. *Male rats consumed a diet containing 0, 12, or 48 percent sucrose on days 16 to 30 of life. Thereafter, they had simultaneous access to all three diets until day 63. No relationship was detected between sucrose consumption early in life and subsequent preference for sucrose. The onset of puberty was associated with a decreased appetite for sucrose among animals of both sexes.*

It is widely believed that the consumption of sucrose during infancy and early childhood is associated with a preference for sweet foods later in life. Although there is considerable evidence that a preference for sweet flavors can be detected in many mammals (including humans) during the first days of life (*1*), we are unaware of any published data concerning the effect of sucrose consumption by infants on their food preferences as adults. In the present report we examine the relationship between the amount of sucrose provided to nursing and immature rats and their elective consumption of sucrose later in life.

In order to choose the amounts of sucrose to include in the test diets and the ages at which to examine feeding behavior, we had first to characterize the ontogenesis of sucrose preference in our experimental animals (Sprague-Dawley rats; Charles River Breeding Laboratories). We therefore measured the quantities of sucrose consumed by male and female rats, from 21 to 63 days of age, given a choice of isocaloric diets with or without sucrose (*2*). On each day, food intake was measured and the position of the food cups was rotated. Sexual maturation was identified in males by the descent of the testes and in females by vaginal opening. The study was repeated three times.

Both male and female rats showed a significant preference for the sucrose-containing diet prior to sexual maturation (Table 1). The appearances of testicular descent (at days 37 to 38) and of spontaneous vaginal opening (at days 39 to 41) both coincided with marked decreases in elective sucrose consumption ($P < .001$) to levels that persisted for the duration of the experiments.

Earlier studies, in which the consumption of a saccharin solution as an index of preference for sweets was used, were interpreted as indicating that immature rats of both sexes reject sweet foods and that mature female rats have a greater

Table 1. Effect of age and sexual maturation on sucrose consumption by rats given choice of 0 and 24 percent sucrose diets. Male and female rats were housed singly at weaning and given access simultaneously to 0 and 24 percent sucrose diets. The diets were isocaloric and contained similar amounts of protein, fat, vitamins, and minerals (*2*). Food intake was measured daily. The percentage of sucrose consumed was determined by dividing the grams of sucrose (× 100) by the total grams of food consumed. Sexual maturation was noted by testicular descent (in a 36-hour period on days 37 to 38) and by spontaneous vaginal opening (days 39 to 41). Data are presented as means and standard errors of the mean.

Age (days)	Percentage of sucrose consumed	
	Male rats	Female rats
21 to 28	21 ± 1.2	22 ± 1.0
29 to 35	19 ± 1.9	21 ± 1.2
36 to 42	11 ± 0.5*	18 ± 1.9
43 to 49	12 ± 1.0	14 ± 0.7*
50 to 56	12 ± 1.7	15 ± 1.2
57 to 63	14 ± 2.2	14 ± 1.0

*$P < .001$ compared to prepubertal sucrose intake.

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