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Food Deprivation Reveals Strain Differences in Opiate Intake of Sprague-Dawley and Wistar Rats

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CARROLL, M E , M C PEDERSON AND R G HARRISON *Food deprivation reveals strain differences in opiate intake of Sprague-Dawley and Wistar rats* PHARMACOL BIOCHEM BEHAV 24(4) 1095–1099, 1986 —Two groups of naive, male, albino rats derived from different genetic strains (Sprague-Dawley and Wistar) were given a 5 μg/ml etonitazene solution as their only available liquid. Liquid intake and body weights were recorded every 24 hr Etonitazene intake was compared to baseline water intake, and drug intake was then compared when the rats were food deprived (25 sessions) and food satiated (24 sessions) Both groups drank similar amounts of water and etonitazene during the initial food satiation phase, although drug intake was slightly below water intake When they were food deprived, the Wistar group's mean etonitazene intake almost doubled, while the Sprague-Dawley group's drug intake decreased by nearly 50% The etonitazene intake in the Sprague-Dawley group never exceeded that of the vehicle, water; thus, it appeared that the drug was not functioning as a reinforcer Food deprivation increased etonitazene intake above water levels in the Wistar group, indicating that the drug was serving as a reinforcer Both groups showed similar drug effects during food deprivation, such as erratic drinking patterns, self-mutilation and other forms of stereotypy Thus, both strains were sensitive to etonitazene's effects, they appeared to differ only with respect to the reinforcing effects These results suggest that genetically-based differences in the reinforcing effects of drugs may be revealed by food deprivation

Etonitazene Food deprivation Food satiation Genetic differences in drug intake Pharmacogenetics Rats Sprague-Dawley Wistar

FOOD deprivation markedly increases oral and intravenous intake of drugs that are abused by humans (cf. [11]). However, the underlying mechanisms of this effect are not well understood. The original purpose of the present study was to replicate and extend the results of a previous experiment [12] by examining etonitazene self-administration over repeated cycles of food deprivation and satiation. The intent was to determine whether increases in drug intake occur more rapidly after repeated exposure to the drug under food deprivation conditions. In the earlier experiment with Wistar rats [12], an etonitazene solution (5 μg/ml) replaced water in the drinking bottles, and when the rats were subsequently food deprived, their drug intake more than doubled In the present experiment we were not able to replicate this initial finding with Sprague-Dawley rats, in fact, food deprivation decreased etonitazene intake as it does water intake [12, 25, 33] When two additional attempts to replicate the earlier findings failed, it appeared that genetic differences may have been responsible.

Genetically-based differences in drug responsivity have been reported in mice using alcohol (cf. [6]) stimulants [2–4] and opiates [8, 10, 13, 15, 18–21, 27, 30, 35]. Strain differences have also been found in studies with rats using alcohol [17, 23, 24, 29, 30, 34] and opiates [7, 9, 26, 31, 32]. The Sprague-Dawley and Wistar strains are commonly used in behavioral pharmacological research, however, genotype × drug self-administration interactions have not been systematically considered with respect to psychoactive drugs There have been a few reports of genetically-based differences in the sensitivity of Sprague-Dawley and Wistar rats to neurotoxins [24] and morphine [7] However, there have been no reports comparing Sprague-Dawley and Wistar rat strains for self-administration of opiates. The purpose of the present experiment was to compare these two rat strains with respect to the effects of food deprivation on etonitazene intake.

METHOD

Animals

Thirty naive, male rats were used in this experiment. Twenty-one of the rats were of Sprague-Dawley derivation (Bio-Lab, Inc., St. Paul, MN) and nine were of the Wistar strain (Harlan Sprague-Dawley, Inc., Indianapolis, IN). At the start of the experiment the Sprague-Dawley rats ranged in weight from 347 to 390 g, and the Wistar rats ranged from 377 to 442 g. The rats were housed in a temperature (24°C) and humidity controlled room under a 12 hr light/dark cycle with the lights on between 7·00 a m. and 7:00 p.m

Apparatus

Throughout the experiment, the rats were housed in individual stainless-steel wire mesh rat cages. They were re-

moved from the cages for about 20 sec each day to record body weights. The rats were habituated to the handling and weighing procedure for five days before the experiment began. Drinking solutions were presented to the rats in 250 ml glass bottles that were attached to the front of the cages with spring clips. Food (Purina Laboratory Chow) was presented in a food hopper on the outside of the front of the cage, or it was placed inside the cage if the rats appeared to be having difficulty eating due to drug effects.

Procedure

Throughout the experiment, each day between 11:00 a.m. and 12:00 noon bottles were removed from the cages and the amounts consumed were measured and recorded. Corrections for evaporation and spillage were made by placing six bottles on empty cages and measuring changes in liquid volume every 24 hr. The body weight of each rat was then recorded, and liquid was returned to the cage. During this procedure, each rat was without food and liquid for approximately 60 min.

All rats were initially given water while food satiated and baseline liquid intakes were recorded. The Wistar rats (N=9) were then exposed to an etonitazene solution (5 μg/ml) instead of water for five days while they remained food satiated. The Sprague-Dawley rats were divided into two groups, one group (N=10) was food deprived and at the same time water was replaced by an etonitazene (5 μg/ml) solution. They were given 8 g of food (Purina Laboratory Chow) per day until they reached 75% of their free-feeding body weights, and then amounts (usually 14–20 g) necessary to maintain them at those weights throughout a 25-day food deprivation phase. The other group (N=11) also received etonitazene but remained food satiated throughout the experiment. This group's data was used only for a comparison of baseline etonitazene intake during the first five days of food satiation. Subsequently, the Sprague-Dawley group was food-deprived for 37 days, however, data are reported for only the first 25 days as there were no increasing or decreasing trends in liquid intake beyond that point. Subsequently, both groups were food satiated for 24 days. Food satiation was accomplished by providing the rats with unlimited access to laboratory chow in their food hoppers.

Drug Solution

The etonitazene HCL (NIDA Research Triangle Institute) solution (5 μg/ml) was mixed daily from a stock solution containing 10 μg/ml which was mixed weekly in tap water. Concentrations are expressed in terms of the salt.

RESULTS

Figure 1 shows liquid intake for the Sprague-Dawley and Wistar groups during repeated cycles of food satiation, deprivation and satiation. During food satiation, water intake was slightly higher for the Wistar rats. Mean liquid intake decreased only by about 10 ml when the etonitazene solution was introduced while the rats were still food satiated. At the onset of food deprivation, changes in volumes of etonitazene consumed became apparent within a few days. The Wistar rats' mean etonitazene intake steadily increased over the 25 sessions, although individual intakes were highly erratic. By the middle of the food deprivation phase, the Wistar group had nearly doubled its etonitazene intake. At the onset of food deprivation, the Sprague-Dawley rats' mean

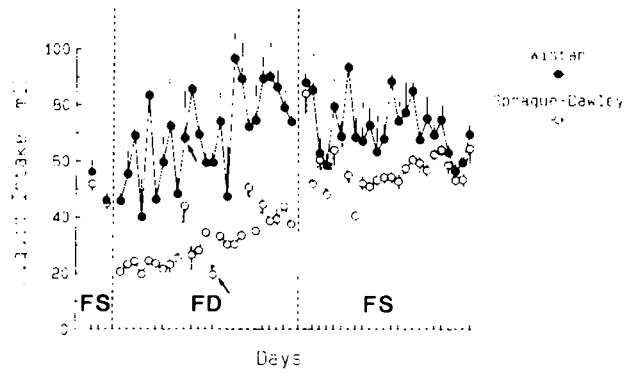

FIG. 1. Mean (±S.E.) liquid intake is presented for groups of Wistar (solid circles) and Sprague-Dawley (open circles) rats during food satiation (FS) and food deprivation (FD). The first unconnected point for each group represents the mean water intake on the last day of the five day water baseline phase. The second point represents the mean etonitazene intake on the last day of the 5 days of etonitazene access during food satiation. Note that this condition was tested in a separate group of 11 rats that served as a food-satiated control for the Sprague-Dawley group. The connected points depict mean etonitazene intakes for 25 sessions of food deprivation followed by 24 sessions of food satiation. The Wistar group consisted of nine rats and the Sprague-Dawley group consisted of ten rats. Arrows indicate the day when all animals in the group had reached their 75% body weights.

etonitazene intake dropped to more than 20 ml below their food-satiation baseline, this amount was less than 50% of their water and etonitazene intake during food satiation. After nine days of food deprivation, mean etonitazene intake gradually increased by approximately 10–15 ml. The food deprivation condition was extended an additional 12 days (the data are not plotted on Fig. 1), but there were no further increases in daily etonitazene intake. By the end of the food deprivation phase, the Sprague-Dawley group's intake had not exceeded water or etonitazene intake during food satiation. All rats in the Wistar group reached their 75% body weight by 10 days and those in the Sprague-Dawley group reached their 75% weights by 14 days following onset of food deprivation. No systematic changes in drinking were observed in either group when the rats were fed more than 8 g of food to maintain them at their 75% weights.

When the rats were food-satiated, etonitazene intake increased substantially in the Sprague-Dawley group. Etonitazene drinking then stabilized at a level slightly higher than the food-satiation etonitazene baseline. The Wistar group continued to drink large quantities of etonitazene and to show the highly erratic drinking patterns while food satiated, however, mean intake and individual variability returned to slightly higher than baseline levels by the end of the 24 food satiation sessions.

The high intersubject variability of the Wistar group was a result of an erratic drinking pattern found in almost all of the rats in the group. The Wistar rats typically drank large volumes of the etonitazene solutions on alternating days. Several rats consumed over 200 ml of the etonitazene solution on alternating days or every third day. This oscillating pattern is only partially revealed in Fig. 1, since means are presented and the rats' oscillating patterns were not synchronized. Figure 2 presents data for an individual rat from each group.

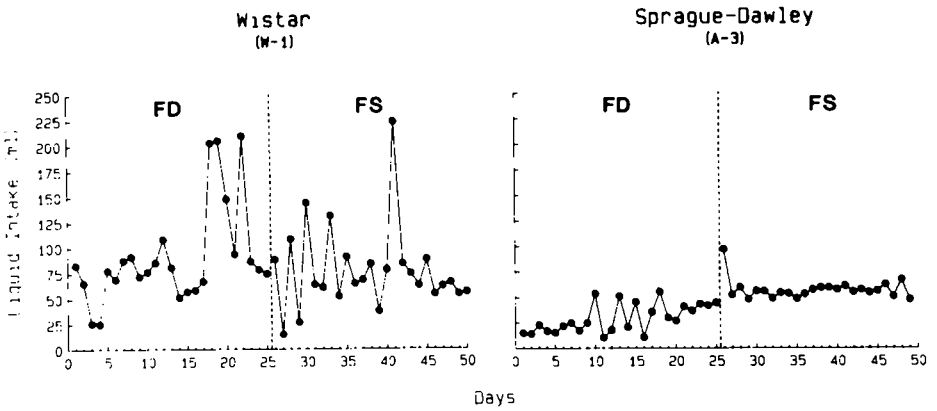

FIG 2 The amount of etonitazene consumed per 24 hr is presented for 25 successive days when the rats were food deprived (FD, left frame) and 24 or 25 successive days when they were food satiated (FS, right frame) Data are from an individual rat in each group (W-1 and A-3) that was selected for liquid intake that was most representative of its group mean and a drinking pattern that was most characteristic of the group

TABLE 1

MEAN 24-HR LIQUID INTAKE (ml/kg) AND ETONITAZENE (5 μg/ml) INTAKE (mg/kg) DURING THE LAST FIVE DAYS OF SEQUENTIAL FOOD SATIATION AND DEPRIVATION PHASES FOR WISTAR AND SPRAGUE-DAWLEY RATS*

		Feeding Condition				
			Food Deprivation		Food Satiation	
Rat Strain		Food Satiation (baseline)	Intake	% Increase†	Intake	% Increase
Wistar	ml/kg	133 8	291 4	117 8	161 1	20 4
	mg/kg	0 7	1 5	117 9	0 8	19 4
Sprague-Dawley	ml/kg	117 2‡	147 9	26 1	147 3	25 6
	mg/kg	0 6	0 7	25 4	0 7	25 4

*Each mean consists of 45, 50, or 55 values (9, 10 or 11 rats × 5 observations each)
†Percent increase over baseline
‡This condition was tested in separate group of 11 rats that served as a food-satiated control for the Sprague-Dawley group

and illustrates the different patterns more clearly. Etonitazene intake for a single rat in each group is presented for the 25 food deprivation sessions and the 24 food satiation sessions, respectively. The individual rats shown here were selected as those whose intakes were closest to the mean and whose patterns were typical of the largest proportion of the group The highly variable pattern of etonitazene drinking for the Wistar group began almost immediately, and increased throughout the experiment The Sprague-Dawley group showed little daily variability for about the first 8–10 days, and then small increases in variability and etonitazene intake until the end of the food deprivation phase.

The weights of each group of rats were changing at different rates throughout the experiment as a function of the food deprivation and satiation conditions, therefore, mean liquid intake as a dependent measure is an underestimate of the amount of drug consumed when body weight is not taken into consideration. Thus, the amount of drug consumed (mg/kg) as a function of rat strain and feeding condition is presented in Table 1

In addition to the large quantities of etonitazene consumed and erratic drinking patterns, other changes in behavior were seen during the food-deprivation phases. Stereotypy occurred in all rats in both groups from the onset of food deprivation It was predominately characterized by self-mutilation, specifically biting of the front paws. By the end of 25 days of food deprivation, all rats in both groups had chewed all digits off the front paws The rats also engaged in rocking behavior and biting the grid floor and front of the cage. Self-mutilation became progressively more severe as these high rates of drinking emerged in the Wistar Group. The rats drinking large amounts in the Wistar group appeared to be more heavily intoxicated than the other Sprague-Dawley rats. Each group had initially consisted of eleven rats, and two of the Wistar rats died. One rat died in the Sprague-Dawley group. Self-mutilation and other stereotyped behavior decreased abruptly when the rats were food satiated. While there were large differences between the total etonitazene intake and the amount of drug consumed (mg/kg) between the Wistar and Sprague-Dawley rats, the onset, time course and severity of self-mutilation were similar in most rats.

DISCUSSION

During food deprivation mean etonitazene consumption nearly doubled in the Wistar group, but the Sprague-Dawley group's mean drug intake remained below baseline water and etonitazene levels During the subsequent food satiation phase, the Wistar group's mean intake decreased but remained at a level that was slightly above the amount the group had consumed prior to food deprivation When etonitazene intake was considered in terms of mg/kg of body weight, the Wistar group showed more than a two-fold increase in the amount of drug consumed during food deprivation while the Sprague-Dawley group revealed a small increase (25%) that developed toward the end of the deprivation phase and continued throughout the satiation phase. The results of the present experiment suggest that there is a genetic component that interacts with the effect of food deprivation on etonitazene consumption Food deprivation appears to be an important factor responsible for high levels of etonitazene intake in Wistar rats but not in Sprague-Dawley rats

The results of the Wistar group agreed closely with data reported earlier in which etonitazene intake nearly doubled during a food deprivation phase [12] The time course and daily patterns of etonitazene intake found in the present experiment were also similar to those reported in the earlier study. However there was a difference in the two experiments in terms of the overall amount of liquid consumed Throughout all phases of the present experiment the Wistar and Sprague-Dawley rats drank almost 50% more water and etonitazene than the Wistar rats in the earlier report [12] Methodological variations that may have accounted for these differences are that the rats used in the present experiment weighed slightly more, and laboratory chow (4–5 g blocks) was used instead of 45 mg pellets (Noyes) as in the earlier study [12]. The Sprague-Dawley group consumed baseline quantities of water and etonitazene that were similar to those of the Wistar rats, thus the decrease in etonitazene intake due to food deprivation could not be explained by differences in baseline water intake The results of the Sprague-Dawley group were very similar to a group in the previous experiment that received water during food deprivation [12], and to the results of other studies investigating the effects of food deprivation on the water intake of rats [25,33] While the Sprague-Dawley group drank considerably less drug than the Wistar group during food deprivation, they did show drug effects that were similar to the Wistar group. Food deprivation produced an erratic drinking pattern in both groups and that pattern was similar to what had been reported earlier [12, 14, 28] There were also findings of self-mutilation and other forms of stereotypy in the two groups As in earlier experiments [12, 14, 28], these changes appeared to result specifically from the combination of food deprivation and etonitazene drinking. That similar drug effects emerged in both groups suggests that in some respects, they were equally sensitive to some effects of the drug but not to the reinforcing effects

Food deprivation produces increased drug self-administration and drug-reinforced operant behavior under a wide variety of conditions For instance, marked increases in drug intake due to food deprivation occur with drugs from many pharmacological classes such as stimulants, sedatives, hypnotics and opiates, and this effect has been demonstrated with a number of species and in several laboratories [11] There have been only a few limitations identified with the food deprivation effect Food deprivation selectively produces increases in drug intake, it does not increase general activity, water drinking or operant behavior reinforced by delivery of the vehicle (water or saline via the oral or intravenous routes, respectively) It appears that food deprivation increases drug intake only when a drug can be independently demonstrated to function as a reinforcer For example, food deprivation generally does not increase self-administration of drugs such as intravenously-delivered methadone, nicotine, tetrahydrocannibinol or orally-delivered cocaine or phencyclidine which have been difficult to establish as reinforcers in laboratory animals [12]

The present study has provided an additional limitation of the food deprivation effect (i.e , genetic strain) It is possible that etonitazine does not function as a reinforcer for the Sprague-Dawley rats, as food deprivation did not increase self-administration It is generally accepted that a drug is functioning as a reinforcer when intake of the drug solution exceeds that of the vehicle (i e , water) Although etonitazene intake increased slightly over time in the Sprague-Dawley group, their drug intake did not exceed the water baseline levels Furthermore, etonitazene intake in the food-satiated control group of Sprague-Dawley rats (data not included) did not exceed the water baseline On the contrary, in the earlier experiment with Wistar rats, a food-satiated control group's etonitazene intake surpassed the baseline water levels [12] Thus, it is likely that etonitazene functions as a reinforcer for food satiated Wistar rats, and food deprivation enhances the reinforcing effects

The present results concur with earlier findings in a study of etonitazene intake in two mouse strains (C57BL/6J and DBA/2J) during food satiation and deprivation [20] While food satiated, the DBAs showed an aversion to etonitazene compared to the C57's slight preference over water Food deprivation further decreased etonitazene intake in the DBA's, but it markedly enhanced drug intake in the C57 group An earlier study showed a positive preference for a morphine and saccharin solution in C57s and an aversion in DBAs [22] While there is an extensive literature demonstrating mouse and rat strain differences in alcohol preference (cf [10,16]) there are only a few pharmacogenetic studies with rats concerning other drugs of dependence (e g , [10, 26, 32, 35], however, reports concerning the self-administration of opiates and drugs other than alcohol in rats are still lacking There have been only a few studies specifically comparing drug effects in the Sprague-Dawley and Wistar strains Using observational measures Borgen and coworkers [7] found that morphine-treated Wistar rats were more aggressive than Sprague-Dawleys Melchior and Myers [24] found drug strain interactions in the way the neurotoxin 5,6-DHT affects alcohol preference in Sprague-Dawleys but not in Wistars The baseline alcohol preference in Wistars was already elevated over that of the Sprague-Dawleys Reports of Wistar and Sprague-Dawley strain differences in alcohol preference have yielded conflicting results, ranging from a greater alcohol preference in Wistars [24] to no clear preference [1,36], however, in these studies the animals typically have been tested while food satiated The results of the present experiment suggest that food deprivation may be useful tool for revealing genetic differences in the acquisition and maintenance of drug self-administration behavior

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