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Failure of Rats Deprived of Water to Increase Food Intake During Glucoprivation Induced by 2-Deoxy-D-Glucose[1]

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WATSON, P. J. AND M. D. BIDERMAN. *Failure of rats deprived of water to increase food intake during glucoprivation induced by 2-deoxy-D-glucose.* PHARMAC. BIOCHEM. BEHAV. 17(5) 955–959, 1982.—Thirsty rats denied access to water did not significantly increase their food intake following the glucoprivic stimulus provided by 750 mg/kg 2-deoxy-D-glucose (2-DG). In a second study, subjects were made hypodipsic through adulteration of their water supply with 0.2% w/v quinine hydrochloride; and they too displayed glucoprivic feeding deficits at 250 mg/kg, 500 mg/kg, and 750 mg/kg dosages. A reduced ability to ingest fluids therefore can inhibit 2-DG-induced eating when rats are examined after experience with water restriction schedules. These data consequently suggest that caution may be necessary in interpreting post-lesion disruptions of 2-DG glucoprivic feeding when severe water intake deficits are also observed.

2-Deoxy-D-glucose Food intake Thirst Glucoprivation Lesion effects

INJECTIONS of 2-deoxy-D-glucose (2-DG) result in a reduced ability of cells to utilize glucose, and animals begin to eat in response to this drug-induced glucoprivation [20]. Brain lesions at such sites as the lateral hypothalamus [6], zona incerta [21], and globus pallidus [12] interfere with this glucoprivic feeding; and data from these investigations are viewed as an indication that the damaged neural systems help control an organism's responsivity to glucoprivation.

Detailed analyses of post-lesion behavioral changes recently have emphasized the difficulties involved in differentiating primary lesion from secondary symptom interaction effects. As only one example, lateral hypothalamic (LH) lesions yield a lowered body weight level in rats [16]; and while this reduction may reflect a direct lesion influence on specific weight regulatory behavioral mechanisms [10], it also may arise at least in part as a side effect produced by such other symptoms as motor debilitation [1], finickiness and adipsia [14], sensory in-attention [13], arousal deficits [22], and an acute aphagia which necessitates forced-feeding procedures [19]. The existence of potential symptom interaction effects means that confident identification of a primary lesion effect will require demonstration of its independence from other lesion-induced changes.

With the disruption of glucoprivic feeding that follows some brain damage. it may be necessary to explore possible symptom interaction effects because some of the lesions which cause this deficit also reduce water ingestion (e.g., [6]). An inability to drink normal amounts of water inhibits ad lib food intake in neurologically intact subjects [5]; and the apparent glucoprivic deficits of lesioned animals theoretically could reflect at least in part a reduced capacity to ingest fluids. The fact that 2-DG alone may increase thirst [18, 20, 27] suggests further the possibility that incapacitation of drinking response systems could help mediate inhibition of glucoprivic feeding. This investigation used neurologically intact rats to determine if 2-DG-induced eating is disrupted by an inability to drink normally. Clearly, such an outcome would not prove that disruptions in drinking behavior cause lesion-induced 2-DG hyporesponsivity; but it would reveal the need of researchers to consider employing water-deprived yoked controls in studies that observe simultaneous glucoprivic and fluid ingestive deficits.

EXPERIMENT 1

In a previous study, hypodipsic rats ate like controls following 2-DG treatment [25]. These animals had not been water deprived and were presented with a quinine adulterated fluid. Since neurologically intact rats maintain a body water surplus [7], the experimental subjects of this previous study may not have experienced as strong a state of hydrational need as lesioned animals. Water-deprived rats in the current experiment were given no opportunity to drink after 2-DG injections.

METHOD

Eighteen experimentally naive adult male Long Evans rats served as subjects. They had been raised in the departmental animal colony and weighed from 406 to 540 g. Subjects were individually housed and tested in 7×7×9.5 in. stainless steel cages that were kept in a room in which temperatures were thermostatically controlled at 68° F. Lighting

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TABLE 1
HOURLY FOOD INTAKE IN GRAMS/KILOGRAM BODY WEIGHT* FOR DEPRIVATION AND NO-DEPRIVATION GROUPS FOLLOWING 2-DG AND SALINE INJECTIONS

Group	Session	Hour 1	2	3	4
Deprivation	2-DG	1.30 ± 0.42	3.07 ± 1.14	1.47 ± 0.39	1.08 ± 0.40
	Saline	1.26 ± 0.69	1.40 ± 0.60	1.11 ± 0.31	2.57 ± 1.03
No-Deprivation	2-DG	3.40 ± 1.15	5.47 ± 1.20	5.18 ± 1.17	1.78 ± 0.80
	Saline	2.12 ± 1.00	2.43 ± 0.72	1.02 ± 0.44	3.62 ± 1.26

*Values represent mean±S.E.M.

was automatically turned on at 8:00 hr and turned off at 20:00 hr, and experimental procedures began at 13:00 hr.

Animals were randomly assigned to the Deprivation (N=9) or the No-Deprivation (N=9) Group. On the first three days, rats were adapted to the home cages, and water deprivation procedures began for the experimental group immediately after the subjects were weighed on Day 3. Testing began with an adaptation session conducted on Day 8. Each rat was removed from its home cage, injected intraperitoneally with a physiological saline solution, and placed in a testing cage immediately above or below the home cage. Purina Lab Chow pellets, measured to the nearest 0.1 g, were made available in the testing cage; and at hourly intervals until subjects had been examined for four consecutive hours, the uneaten food was removed, measured, and replaced with a fresh supply. Precautions were taken to collect all food spillage. For Deprivation Group subjects, no water was ever made available during this 4-hr interval; but these rats were given 30 min access to water when returned to the home cage. A saline control session occurred on Day 9, and the procedures of the adaptation session were replicated. The same procedures were again used on Day 10 except that 750 mg/kg 2-DG injections (Sigma, 10% w/v in distilled water) were administered. On the two previous physiological saline treatment days, isovolemic injections had been utilized. Food intakes during the Day 9 saline session and during the Day 10 2-DG session were compared. The amount eaten was expressed as g of food/kg body weight to help control for the deprivation-induced weight differential across groups.

RESULTS

By Day 10, subjects in the Deprivation Group were at 90% of their Day 1 body weight while nondeprived rats weighed 107% of this value. Table 1 presents the average hourly food intakes of the two groups during the 2-DG and saline sessions, and it demonstrates that in general greater food intake was displayed by No-Deprivation animals and during 2-DG treatment.

Analysis of these data revealed significant Group, $F(1,16)=9.16, p<0.01$, and Drug, $F(1,16)=10.51, p<0.01$, effects. Of primary interest, however, was the significant Group × Drug interaction, $F(1,16)=7.41, p<0.025$. Correlated t-tests were used to compare the cumulative intakes of saline and 2-DG sessions for each group, and they revealed a drug-produced increase for the No-Deprivation Group, $t(8)=-3.53, p<0.01$, but not for the Deprivation Group, $t(8)=-0.49, p>0.05$. In addition, the Drug × Hour interaction, $F(3,48)=5.51, p<0.01$, was significant while the hour, $F(3,48)=0.99, p>0.05$, the Hour × Group, $F(3,38)=0.19, p>0.05$, and the Drug × Hour × Group, $F(3,48)=1.15, p>0.05$ effects were not.

EXPERIMENT 2

In the first experiment, water-deprived rats were denied the opportunity to drink; and they did not display glucoprivic feeding. Such data are only suggestive, however, until a wider range of drug dosages is examined, particularly since the Deprivation subjects lost weight and consequently received relatively reduced amounts of the drug. Three different 2-DG dosages were used in this second study, and fluid restriction experience and reduced drinking behavior were produced through quinine adulteration of water. Neurologically intact rats presented with adulterated water are more analogous to LH lesioned subjects, for example, which appear to find water unpalatable during the post-surgery intervals when their drinking behavior is most disturbed [6].

METHOD

Forty adult female rats with weights ranging from 227 g to 360 g served as subjects. Their histories were similar to the animals of the first experiment, and they were housed in the same laboratory environment.

Following several weeks adaptation to the individual home cages, the subjects were randomly assigned to one of eight equally sized groups (N=5). Half the animals were placed in the Adulteration (AD) Groups with the other half in the No-Adulteration (NAD) Groups. Within these groups, rats were then assigned to the saline, 250 mg/kg, 500 mg/kg, and 750 mg/kg treatment conditions.

On Day 1, AD subjects were provided with a water supply adulterated with 0.2% w/v quinine hydrochloride (Sigma) while NAD animals continued to receive tap water. Both groups received food ad lib. Daily body weights and food intakes were measured to the nearest g over the next five days. Fluid intakes were also estimated by weighing water bottles to the nearest g at approximately 13:00 hr each day. A large number of the AD rats reacted to the bitter fluid by vigorously biting at the drinking tube and bottle; and as a result, an indeterminant amount of fluid was spilled and could not be recorded. This aversion reaction also occurred during the 2-DG experimental session; and as a consequence, fluid intake comparisons among the AD groups were

TABLE 2

FLUID AND HOURLY FOOD INTAKES* OF AD AND NAD ANIMALS FOLLOWING SALINE OR 2-DG INJECTIONS

Group†	Fluid Intake	Hourly Food Intake 1	2	3	4	Total
AD-Saline	8.80 ± 2.35	0.78 ± 0.50	1.42 ± 0.29	1.26 ± 0.41	0.46 ± 0.21	3.92 ± 0.53
AD-250	3.80 ± 1.50	0.26 ± 0.19	1.54 ± 0.30	1.38 ± 0.46	0.38 ± 0.29	3.56 ± 0.76
AD-500	4.40 ± 1.43	2.14 ± 0.79	1.38 ± 0.65	1.78 ± 0.74	0.94 ± 0.58	6.24 ± 0.92
AD-750	5.20 ± 1.71	0.06 ± 0.06	2.00 ± 0.57	1.08 ± 0.29	0.64 ± 0.34	3.78 ± 0.58
NAD-Saline	8.80 ± 2.57	0.94 ± 0.94	1.48 ± 0.55	1.72 ± 1.04	2.50 ± 0.67	6.64 ± 1.84
NAD-250	7.20 ± 2.22	9.50 ± 2.12	5.60 ± 0.93	2.74 ± 1.03	1.46 ± 0.65	19.30 ± 2.81
NAD-500	9.00 ± 1.92	2.12 ± 1.26	6.06 ± 1.08	4.22 ± 0.92	2.32 ± 0.65	14.72 ± 2.20
NAD-750	11.60 ± 1.57	0.32 ± 0.32	5.20 ± 0.97	6.64 ± 2.17	2.16 ± 0.82	14.32 ± 2.77

*Fluid Intakes = mean g ±S.E.M. and Food Intakes = mean g/kg ±S.E.M.

†AD, but not NAD, animals received quinine adulterated water supplies before and after injections of saline, 250 mg/kg 2-DG, 500 mg/kg 2-DG, or 750 mg/kg 2-DG.

made problematic. However, comparisons between AD and NAD groups remained possible at a relative level.

Experimental procedures were conducted after the AD animals had experienced five days acess to the adulterated fluid. These procedures replicated those of the first study with a few exceptions. All testing was conducted in the home cage, and adulterated fluid or water was available ad lib. Fluid consumption, unlike food intake, was recorded for the entire four hours, rather than for each hourly interval. Subjects were injected with physiological saline, 250 mg/kg 2-DG, 500 mg/kg 2-DG, or 750 mg/kg 2-DG depending on group assignments; and saline injections were isovolemic with the 500 mg/kg dosage. Once again, food intake was expressed as g/kg body weight.

RESULTS

During the five days of AD subject adaptation to adulterated fluid, these animals reduced food and fluid intake and lost weight steadily. AD food ingestion averaged 5.3 g on the day before experimental procedures were conducted, and this amount was considerably below the 19.1 g of the NAD rats. AD fluid intake was down to 18.0 g compared to the NAD 37.7 g, and the AD rats averaged 85% their initial weight while the NAD value was 102%. All these data represented statistically significant differences.

Measures of food and fluid intake during the experimental session are summarized in Table 2, which reveals an overall tendency of AD subjects to eat and to drink less that the NAD animals. Analysis of the food intake data was accomplished with a 2×4×4 ANOVA that examined, the Fluid, Drug, and Hour effects. AD eating was significantly below that of the NAD groups, $F(1,32)=54.52$, $p<0.001$, and food ingestion varied with the 2-DG treatment, $F(3,32)=4.54$, $p<0.01$. Of greatest importance, however, was the observation that the Fluid and Drug effects interacted, $F(3,32)=4.50$, $p<0.025$. Significant Hour, $F(3,96)=6.33$, $p<0.01$, Drug × Hour, $F(9,96)=4.59$, $p<0.001$, and Fluid × Drug × Hour, $F(9,96)=5.40$, $p<0.001$ effects were also obtained, but the Fluid × Hour interaction was not significant, $F(3,96)=1.09$, $p>0.05$.

Duncan's Range Tests with $p=0.05$ were utilized in post hoc analyses designed to clarify the nature of the Fluid × Drug interaction. All four AD groups ate statistically comparable amounts of food which were not significantly different from the NAD-Saline intake. The three drug-treated NAD groups displayed essentially equal intakes that were significantly elevated over that of the other groups. These findings thus support the conclusion that water adulteration depressed subject responsivity to the 2-DG glucoprivic feeding stimulus.

A 2×4 (Fluid × Drug) ANOVA was employed to analyze the fluid intake results. AD animals drank less, $F(1,32)=6.79$, $p<0.025$, but no Drug, $F(3,32)=1.23$, $p>0.05$, nor Fluid × Drug, $F(3,32)=0.95$, $p>0.05$, effects were discovered.

GENERAL DISCUSSION

Experience with fluid restriction regimens apparently combines with an inability to drink normal amounts of water to cause a reduced sensitivity to the glucoprivic stimulus afforded by 2-DG. This lowered responsivity was displayed by rats which had been water deprived and then denied access to fluid and by aminals which were made hypodipsic prior to and during testing procedures through quinine adulteration of their water supply. The inhibition effect was not limited to a specific dosage of 2-DG, but was observed with injections ranging from 250 mg/kg to 750 mg/kg. These data therefore indicate that in some circumstances disrupted drinking behavior can inhibit not only ad lib food intake, but the 2-DG glucoprivic response as well.

Specification of the exact physiological and behavioral mechanisms underlying these results is not possible based on the findings of this investigation alone, and a number of possibilities may deserve consideration. First, it might be argued that the ability of 2-DG to elicit eating requires that food be "rewarding." Palatability factors are important determinants of the 2-DG response [8,9], and rats unable to drink normal amounts of water could find dry lab chow to be aversive. Animals in such a situation might meet the glucoprivic challenge through a physiological strategy that mobilizes stored nutrients rather than through a behavioral strategy that redresses the imbalance through intake of new foodstuffs. The data of this study do not enable definitive elimination of this possibility; nevertheless, its plausibility

appears weakened by a previous demonstration [25] that hypodipsia alone is not a sufficient condition for disrupting 2-DG-elicited eating.

A second possibility is that fluid restriction regimens produced a body water deficit and that the consequent dehydration directly inhibited food intake through the interactive nature of body fluid and nutrient regulation. Since no attempt was made to measure the body fluid status of experimental subjects, such an explanation cannot be directly supported. Further, this hypothesis could be countered with the argument that renal systems were effective enough in conserving body water to prevent a state of true dehydration. Evidence contraindicating this alternative comes from demonstrations of body fluid depletions after water deprivation [11] and quinine adulteration [15,17]. Nevertheless, the present experiments did not demonstrate water loss with the particular subjects and procedures utilized.

The absence of body fluid measures becomes even more important in light of the unpublished observations of Kanarek [9] that rats water-deprived to 85% of control weights increased their food intake following 2-DG injections. These data were presented within the context of an analysis of why body weight reduction [19] is not a sufficient stimulus for blocking 2-DG responsivity, and that discussion is relevant in this study as well. However, Kanarek's finding is in obvious contradiction to the results reported here. Suggestions about the cause of the discrepancy are difficult in the absence of detailed procedural information, but one possibility hinges on the use of different subjects. Individual [2] and strain [23] variability may exist with regard to the relative reliance of animals on physiological and behavioral responses to hydrational challenges. Kanarek may have employed animals more fully committed to a physiological strategy while the rats of this study may have been more dependent on a behavioral approach. Consistent with this idea is the observation that control subjects in other experiments conducted in the Kanarek lab [9] did not increase fluid intake following 2-DG or insulin. This failure is interesting because both drugs produced significant elevations in food intake which presumably necessitated some type of compensatory action by fluid homeostatic controls and because insulin alone [3,4], like 2-DG [18, 20, 27], can trigger drinking behavior. Such an analysis is weakened by the failure of rats in the second experiment to drink more after 2DG; however, animals of the same strain in this laboratory have increased water intake following glucoprivation [25]. Clearly, more detailed investigation is needed into the possible contribution of hydrational factors to glucoprivic responsivity.

One important implication of these findings may be that they suggest the need for caution in interpreting some lesion-induced disruptions of 2-DG glucoprivic feeding (e.g., [6]). When brain damage results in severe water intake deficits, the accompanying inability to respond normally to 2-DG may be mediated at least in part by the loss of drinking controls. The fact that the AD-500 rats in the second study increased food intake, though nonsignificantly so, relative to the AD controls suggests that the inhibition effect may not be absolute; and further investigation into this possibility is needed. Nevertheless, the data indicate that future experiments may find it necessary to use controls yoked to lesioned animals in terms of water intake before definitive statements can be made about the quantitative or qualitative effects of brain damage on 2-DG-induced eating.

However, at least four considerations deserve emphasis with regard to generalizing these data to the lesion literature. First, presentation of palatable liquid diets ameliorates at least some lesion-induced glucoprivic deficits [9], and the independence of palatability and hydrational factors in mediating this effect needs to be explored more fully. Secondly, as forewarned in the introduction, this study does not prove that drinking deficits underlie glucoprivic hyporesponsivity in brain damaged rats. LH animals, for example, exhibit a wide range of impairments [6, 10, 13, 14, 22]; and definitive proof of the necessity and sufficiency of any symptom or combination of symptoms in producing loss of glucoprivic reactivity would require direct and careful analysis in studies employing lesioned subjects. Thirdly, the thirsty animals in the present experiments were very roughly analogous only to lesioned rats displaying severe disruptions in drinking behavior during the intervals immediately after surgery. The subjects of the first study were procedurally prevented from drinking while those of the second experiment drank minimal amounts. In contrast, LH lesioned rats are initially adipsic but eventually do recover some limited water ingestive capabilities [6]. Nevertheless, disruption of 2-DG responsivity persists in LH subjects [26], and it remains to be determined if more subtle alterations in drinking behavior could contribute to this longer lasting effect. An exploration of 2-DG effects in rats fully adapted to quinine adulterated water [15,17] therefore would be of interest. Finally, some evidence indicates that the physiological systems mediating glucoprivic feeding elicited by 2-DG and insulin may be at least partially dissociable [24], and a conclusion that insulin-induced feeding would be similarly inhibited by interference with normal drinking behavior would appear premature. Experimental analyses of these issues are currently underway.

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