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Structural Evaluation of Anorectic Action Induced by 1,5-Anhydro-D-glucitol (42036)

K. FUJIMOTO, T. SAKATA, K. TERADA, K. ARASE, M. FUKUSHIMA, AND A. SIMPSON*

*First Department of Internal Medicine, Faculty of Medicine, Kyushu University, Fukuoka, 812 Japan, and *Department of Physiology, Faculty of Medicine, Showa University, Tokyo, 142 Japan*

Abstract. In previous studies, 1,5-anhydro-D-glucitol (1-DG), an endogenous glucose analog, was found to significantly influence physiological feeding behavior. The relationships between the hydroxyl group positions on the pyranose ring carbons and the anorectic action induced by 1-DG and its analogs are discussed. To investigate the effects of these glucose analogs on ingestive behavior, 24 μmole of test solution was injected into the rat third cerebral ventricle immediately before normal eating time, which starts at the beginning of the dark. After initial transient hyperphagia, 1-DG suppressed feeding during the first 12-hr dark period. It prolonged postprandial intermeal interval beginning shortly after injection, but eating rate was not affected and meal size did not decrease until near the end of the normal feeding period. The incidence of drinking episodes decreased concomitant with feeding suppression. Feeding and drinking suppression were also produced by 1,2-dideoxy-D-glucose, 1,3-dideoxy-D-glucose, and 1,4-dideoxy-D-glucose, although they were less potent than 1-DG. They suppressed feeding by prolonging the postprandial intermeal interval, but did not change meal size or eating rate. The anorectic effects of 1-DG were abolished by removal of the hydroxyl group at carbon 6 and by epimerization at carbons 2, 3, and 4. These findings indicate that feeding suppression induced by 1-DG and its analogs is induced mainly by prolongation of the postprandial intermeal interval, and the presence or absence of a hydroxyl group on each carbon of 1-DG is important for its feeding suppression.

In our previous studies (1–3) 1,5-anhydro-D-glucitol (1-DG) was shown to suppress food intake in rats, and we suggested that it provides physiological signals for food intake. In order to investigate mechanisms of feeding suppression produced by 1-DG, the present study was initiated to clarify the relations between the anorectic action of 1-DG and the roles of the respective hydroxyl groups at each carbon of the pyranose ring. Structural analogs of 1-DG were synthesized with an hydroxyl group removed from one or another carbon of the pyranose ring, or with a sterically hindering group introduced by epimerization. The anorectic action of each of these 1-DG analogs was then analyzed, and feeding and drinking patterns were compared with those of 1-DG.

Materials and Methods. *Animals.* Mature male Wistar king A rats, 270–320 g, were used. They were housed in a soundproof room illuminated daily from 0800 to 2000 hr (12/12-hr light–dark cycle) and maintained at 21 ± 1°C with humidity at 45 ± 5%.

Reagents. Test solutions used were 1,5-anhydro-D-glucitol (1-deoxy-D-glucose: 1-DG), 1,5-anhydro-2-deoxy-D-glucitol (1,2-dideoxy-D-glucose: 1,2-DDG), 1,5-anhydro-3-deoxy-D-glucitol (1,3-dideoxy-D-glucose: 1,3-DDG), 1,5-anhydro-4-deoxy-D-glucitol (1,4-dideoxy-D-glucose: 1,4-DDG), 1,5-anhydro-6-deoxy-D-glucitol (1,6-dideoxy-D-glucose: 1,6-DDG), 1,5-anhydro-D-mannitol (1-deoxy-D-mannose), 1,5-anhydro-D-allitol(1-deoxy-D-allose) and 1,5-anhydro-D-galactitol(1-deoxy-D-galactose) (synthesized by Chugai Pharmacological Co. Ltd.).

General procedure. At least 1 week before the testing, all rats were implanted with an intra-third ventricle cannula of 29-gauge stainless-steel tubing. The surgical methods have been described in detail elsewhere (4). At testing time, food intake and body weight had returned to normal. Prior to each experiment all rats were handled for 5 min daily during 5 successive days. Each test was started at 1930 hr. Test rats were intraventricularly infused with freshly prepared test solutions at a rate of 1.0 μl/min. All test solutions were prepared in doses of 2.4 *M* in distilled water. The same volume of 0.15 *M* saline was infused as control. Immediately after the

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experiments, dye was infused into the cannulae to verify their position in the third ventricle.

Measurement of 24-hr powdered food consumption. The rats were allowed *ad lib* access to tap water and powdered Clea rat chow CE-2 (Japan Clea Inc. Ltd.). Food consumption and body weight were measured daily at 2000 hr immediately before the dark period. Special feeding boxes were used to facilitate accurate measurement of powdered food consumption (5). After a 3-day adaptation period, baseline data were taken for 3 days. Based on this data, the rats were divided into nine groups of four rats each: a 1-DG group, one group for each of the four kinds of dideoxy-D-glucose (DDG), one for each of the three kinds of 1-DG epimers, and the saline control group. The groups were matched on the basis of mean food intake and body weight. Observations of daily food intake and body weight were carried out for 48 hr before and 48 hr after infusion. Values are expressed as differences from the corresponding baseline levels before administration of the test solutions. Statistical evaluation was carried out using Welch's method.

Analyses of feeding and drinking patterns. Each rat was housed in a 30 × 25 × 25-cm testing chamber equipped with a pellet sensing eatometer (6) and a drinkometer (7), devices for automatically and continuously recording food and water consumption. Rats were allowed free access to standard pellet rat chow (mean weight, 48.2 ± 0.6 mg ranging from 46 to 55 mg) and tap water (mean droplet volume, 63.2 ± 0.9 μl ranging from 56 to 70 μl). Food pellets and water droplets consumed were automatically recorded in a minicomputer. The system has been described in detail elsewhere (8). After rats were adapted to the chamber for 1 week, data were recorded during 2 days preceding and following infusion of the test solutions. Matched on the basis of food consumption and body weight according to the preinfusion data, rats were divided into five groups of four each. The test solutions were 1-DG, 1,2-DDG, 1,3-DDG, 1,4-DDG, and saline.

(i) One hour cumulative food consumption during the first dark period. Changes in food intake following the infusion of test solutions were analyzed in terms of 1-hr cumulative measures during the first dark period. Values were expressed as differences from the corresponding initial levels before injection. Statistical evaluation was carried out using analysis of variance with replication.

(ii) Analyses of meals during the first dark period. Meal size was expressed as number of pellets and postprandial intermeal interval as minutes. Eating rate obtained from meal size divided by meal duration was expressed as number of pellets per minute. The meal parameters were defined to accommodate rat to rat episodes in which more than 10 pellets were consumed and intervals exceeding 10 min (9). Statistical evaluation was carried out using Student's *t* test.

Results. *Effects on 24-hr consumption of powdered food.* The effects of powdered food intake and body weight on four kinds of dideoxyglucose (DDG) and saline are shown in Table I. Saline controls did not change food intake or body weight after injection (basal levels of food intake, 23.3 ± 0.6 g;

TABLE I. FOOD CONSUMPTION AND BODY WEIGHT DIFFERENCES FROM PRETREATMENT LEVELS AFTER INTRA-THIRD VENTRICLE INFUSION OF 1-DEOXY-D-GLUCOSE AND DIDEOXY-D-GLUCOSE

Treatment	Day of infusion		Day after infusion	
	Food intake (g)	Body weight (g)	Food intake (g)	Body weight (g)
1-Deoxy-D-glucose	−12.8 ± 0.5**	−15.3 ± 1.4**	−2.7 ± 1.2	−10.5 ± 0.6**
1,2-Dideoxy-D-glucose	−5.7 ± 0.7*	−8.0 ± 2.9	−1.6 ± 1.1	−1.8 ± 4.4
1,3-Dideoxy-D-glucose	−3.9 ± 0.9*	−6.3 ± 1.3	+0.2 ± 1.0	−0.8 ± 2.2
1,4-Dideoxy-D-glucose	−6.3 ± 1.3*	−6.5 ± 1.7	−0.2 ± 0.6	+3.3 ± 1.9
1,6-Dideoxy-D-glucose	−0.3 ± 1.1	+1.6 ± 1.3	−0.6 ± 1.1	+2.3 ± 1.2
Saline	+0.2 ± 0.4	+2.5 ± 4.5	−0.4 ± 0.5	+2.0 ± 0.9

* $P < 0.05$, ** $P < 0.01$, compared to the corresponding saline controls.

body weight, 311.3 ± 6.0 g). On the first day after infusion, 1-DG significantly decreased food intake below the control level (t = 15.0, $P < 0.01$). On the second day, food intake returned to the baseline level, 23.2 ± 0.8 g. The first day after 1-DG infusion, body weight also diminished significantly compared to that of controls (t = 15.0, $P < 0.01$) and this effect continued into the second day (t = 9.9, $P < 0.01$) (basal level, 304.3 ± 11.4 g). On the first day after administration of 1,2-DDG, 1,3-DDG, and 1,4-DDG, food intake decreased (t = 4.2, 3.8, and 4.1, respectively, $P < 0.05$ for each), but weight loss was not statistically significant. Initial body weights of the 1,2-DDG, the 1,3-DDG, and the 1,4-DDG groups were 313.5 ± 14.3, 289.8 ± 11.8, and 300.5 ± 0.7 g, respectively. On the second day, feeding returned to the initial levels. Initial food intake of the 1,2-DDG, 1,3-DDG, and 1,4-DDG groups was 23.6 ± 1.2, 25.9 ± 0.8, and 24.5 ± 0.5 g, respectively. 1,6-DDG had no influence on food intake or body weight (initial intake, 24.4 ± 0.5 g; body weight, 307.3 ± 8.7 g).

Table II shows changes in food intake and body weight following administration of three kinds of 1-DG epimers. Infusion of these epimers did not significantly affect food intake or body weight. Basal levels of food intake were 22.2 ± 1.4 g for 1-deoxymannose, 25.0 ± 1.4 g for 1-deoxyallose, and 25.1 ± 1.2 g for 1-deoxygalactose, and basal body weights were 295.3 ± 4.9, 317.3 ± 8.7, and 310.8 ± 8.2 g, respectively.

Effects on feeding and drinking patterns: (i) One hour cumulative food intake during first dark period. Results are shown in Fig. 1. After injection, the 1-DG and the DDG groups ate fewer pellets than the controls: 1-DG vs saline, $F(1, 72) = 30.9$; 1,2-DDG vs saline, $F(1, 72) = 14.5$; 1,3-DDG vs saline, $F(1, 72) = 11.7$; 1,4-DDG vs saline, $F(1, 72) = 12.3$; ($P < 0.01$ for each). The 1-DG group ate less than the DDG groups: 1-DG vs 1,2-DDG, $F(1, 72) = 10.7$; 1-DG vs 1,3-DDG, $F(1, 72) = 24.6$; 1-DG vs 1,4-DDG, $F(1, 72) = 28.0$; ($P < 0.01$ for each). Among the DDG groups, reduction of food intake induced by 1,2-DDG was more potent than that of the others: 1,2-DDG vs 1,3-DDG, $F(1, 72) = 7.2$ ($P < 0.05$); 1,2-DDG vs 1,4-DDG, $F(1, 72) = 10.4$ ($P < 0.01$). The effects of 1,3-DDG and 1,4-DDG did not differ significantly. Of the four test solutions, 1-DG produced the largest anorectic effect.

(ii) Effects on meals during the first dark period. Table III shows the time course of changes in cumulative meal size, postprandial intermeal interval and eating rate in successive 4-hr intervals during the first 12-hr dark period after injection. When compared to controls, postprandial intermeal intervals of the 1-DG and 1,2-DDG groups were prolonged in the first 4-hr cumulative period of 2000–0000 hr (1-DG, t = 18.1; 1,2-DDG, t = 6.8; $P < 0.01$ for each). In the second 4-hr cumulative period of 0000–0400 hr, the postprandial intermeal intervals of 1-DG, 1,2-DDG, 1,3-DDG, and 1,4-DDG were significantly longer than those of the controls (1-DG, t = 5.0, $P < 0.01$; 1,2-DDG, t = 2.5, $P < 0.05$; 1,3-DDG, t = 2.5, $P < 0.05$; 1,4-DDG, t = 2.2, $P < 0.05$). In the third 4-hr cumulative period of 0400–0800 hr, the postprandial intermeal interval was not significantly longer in any of the DDG groups, although the postprandial intermeal interval in the 1-DG group tended to be prolonged (t = 1.9, $P < 0.1$). In contrast to postprandial

TABLE II. FOOD CONSUMPTION AND BODY WEIGHT DIFFERENCES FROM PRETREATMENT LEVELS AFTER INTRA-THIRD VENTRICLE INFUSION OF 1-DEOXY-D-GLUCOSE EPIMERS

	Day of infusion		Day after infusion	
Treatment	Food intake (g)	Body weight (g)	Food intake (g)	Body weight (g)
1-Deoxy-D-mannose	−1.7 ± 0.8	−2.3 ± 1.9	−1.5 ± 0.5	+0.6 ± 0.8
1-Deoxy-D-allose	−1.6 ± 1.2	−1.8 ± 2.5	−0.4 ± 1.3	+2.5 ± 0.8
1-Deoxy-D-galactose	−1.3 ± 1.1	−2.8 ± 2.2	−0.1 ± 0.8	−0.5 ± 1.8
Saline	+0.2 ± 0.4	+2.5 ± 4.5	−0.4 ± 0.5	+2.0 ± 0.9

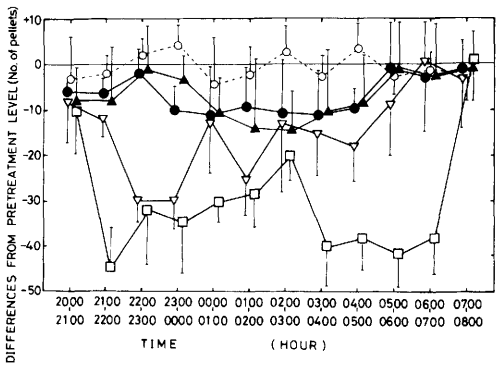

FIG. 1. Time course of changes in food intake during first 12-hr dark period after administration of test solutions. Each number of pellets per hour expressed as 1-hr cumulative differences from corresponding pretreatment levels. □ — □: 24 μmole 1,5-anhydro-D-glucitol (1-deoxy-D-glucose), ▽ — ▽: 24 μmole 1,2-dideoxy-D-glucose, ● — ●: 24 μmole 1,3-dideoxy-D-glucose, ▲ — ▲: 24 μmole 1,4-dideoxy-D-glucose, O - - O: 1.5 μmole saline.

intermeal interval, meal size was not immediately affected by 1-DG injection. It was only in the third 4-hr cumulative period of 0400–0800 hr that meal size decreased significantly ($t = 2.4$, $P < 0.05$). In the DDG groups, meal size showed no change after injection. Neither 1-DG nor three kinds of DDG produced any change in eating rate.

(iii) Effects on the first meal following injection and on the last meal in the dark. The first meal after administration of the test solutions was analyzed in terms of latency to eat from start of injection, meal size, postprandial intermeal interval, and eating rate. The results are shown in Table IV. Latency to the first meal after 1-DG injection was significantly shortened ($t = 2.5$, $P < 0.05$) since feeding occurred immediately after the injection. Neither meal size nor eating rate was affected. However, 1-DG significantly prolonged the postprandial intermeal interval between the first and the second meals ($t = 2.8$, $P < 0.05$). 1,2-DDG, 1,3-DDG, and 1,4-DDG did not affect meal size, eating rate, time of latency to the first meal, or postprandial intermeal interval between the first and the second meals.

The postprandial intermeal interval between the last meal on the injected day and the first meal on the succeeding day was the same length as in the controls (postprandial

TABLE III. FOUR HOUR CUMULATIVE MEAL SIZES (MS), EATING RATES (ER) AND POSTPRANDIAL INTERMEAL INTERVALS (IMI) DURING THE FIRST 12-hr DARK PERIOD AFTER INTRA-THIRD VENTRICLE INFUSION OF 24 μmole TEST SOLUTIONS

Treatment and behavioral item	4 hr period (hr)		
	2000–0000	0000–0400	0400–0800
1-Deoxy-D-glucose			
MS (pellet)	47.0 ± 6.0	43.7 ± 5.4	36.3 ± 4.2*
ER (pellet/min)	2.7 ± 0.4	3.4 ± 0.4	3.0 ± 0.1
IMI (min)	388.0 ± 12.1**	126.4 ± 9.9**	86.3 ± 16.5
1,2-Dideoxy-D-glucose			
MS (pellet)	39.5 ± 4.1	46.8 ± 7.6	46.6 ± 5.8
ER (pellet/min)	2.9 ± 0.4	3.1 ± 0.2	3.1 ± 0.3
IMI (min)	272.4 ± 30.8**	86.0 ± 7.7*	62.3 ± 19.3
1,3-Dideoxy-D-glucose			
MS (pellet)	40.0 ± 4.0	43.3 ± 1.6	51.8 ± 5.1
ER (pellet/min)	2.9 ± 0.2	3.1 ± 0.2	3.2 ± 0.2
IMI (min)	91.8 ± 11.4	90.5 ± 7.2*	37.4 ± 6.7
1,4-Dideoxy-D-glucose			
MS (pellet)	38.0 ± 1.3	44.0 ± 1.9	50.7 ± 4.0
ER (pellet/min)	2.8 ± 0.2	3.1 ± 0.2	3.0 ± 0.1
IMI (min)	90.5 ± 56.1	79.1 ± 2.5*	66.4 ± 6.6
Saline			
MS (pellet)	43.6 ± 7.1	49.0 ± 4.8	51.8 ± 5.5
ER (pellet/min)	2.7 ± 0.2	3.2 ± 0.1	3.1 ± 0.2
IMI (min)	73.0 ± 12.8	56.1 ± 7.0	49.1 ± 12.2

Note. Pellet: number of pellets.
* $P < 0.05$, ** $P < 0.01$, compared to the corresponding saline values.

TABLE IV. CHANGES IN LATENCY TO FIRST MEAL AFTER INJECTION, MEAL SIZE (MS), EATING RATE (ER), AND POSTPRANDIAL INTERMEAL INTERVAL (IMI) TO THE SECOND MEAL

Treatment	Latency (min)	MS (pellet)	ER (pellet/min)	IMI (min)
1-Deoxy-D-glucose	19.9 ± 6.2*	42.8 ± 13.8	2.9 ± 0.2	243.8 ± 55.1*
1,2-Dideoxy-D-glucose	32.1 ± 15.7	37.5 ± 1.4	2.7 ± 0.4	45.6 ± 14.3
1,3-Dideoxy-D-glucose	35.9 ± 7.0	35.8 ± 7.0	2.8 ± 0.3	64.0 ± 7.3
1,4-Dideoxy-D-glucose	34.2 ± 17.0	38.3 ± 6.5	2.7 ± 0.6	63.9 ± 21.5
Saline	40.8 ± 6.3	41.0 ± 2.3	2.6 ± 0.2	61.1 ± 12.8

Note. Pellet: number of pellets. *$P < 0.05$, compared to the corresponding saline controls.

intermeal interval, 645.2 ± 61.8 min) and all other groups. Neither meal size nor eating rate of the last meal of the controls differed from those of the other meals in the dark period (meal size, 50.0 ± 6.1 pellets; eating rate, 2.8 ± 0.8). Meal size, eating rate, and postprandial intermeal interval of the last meal of the 1-DG and DDG groups did not differ significantly from those of the controls.

(iv) Meal and drinking patterns preceding and subsequent to injections. Typical meal and drinking patterns for one rat in the 36 hr preceding and 36 hr following infusion of 1-DG are illustrated in Fig. 2A. Within the first hr after 1-DG infusion, one or two meals were elicited in all four rats tested, but these meals were not accompanied by drinking episodes. No rat took a meal or drank for at least the first 6 hr after the initial hyperphagia. Consequently, the postprandial intermeal interval was prolonged and the meal size decreased in the first dark period after injection of 1-DG. On the second day, this suppression in food and water intake disappeared but not completely. Meal and drinking patterns for 1,2-DDG, 1,3-DDG, 1,4-DDG, and saline-treated rats are shown in Figs. 2B, C, D, and E, respectively. These analogs of 1-DG also suppressed feeding and drinking. Magnitude of suppression was less than that of 1-DG, but 1,2-DDG was the most potent of the three. No suppression of feeding was observed after saline infusion.

Discussion. The results of the present experiments are summarized as follows: (a) After initial slight hyperphagia without drinking, 1-DG produced marked hypophagia during the first 12-hr dark period. It prolonged the postprandial intermeal interval promptly, and meal size of the delayed meal that started 8 hr after the injection was also decreased. (b) Feeding suppression was also observed after the administration of 1,2-DDG, 1,3-DDG, or 1,4-DDG, although they were less potent than 1-DG. Among the DDG groups, 1,2-DDG was a more potent suppressor of feeding than the others. The suppressive effects of these DDG groups were observed as prolonged postprandial intermeal intervals, not as changes in meal size or eating rate. Infusion of 1,6-DDG had no influence in feeding or drinking behavior. (c) Three kinds of 1-DG epimers, 1-deoxymannose, 1-deoxyallose, and 1-deoxygalactose, had no effect on ingestive behavior.

The potent and sustained hypophagia induced by 1-DG in the present experiment was consistent with previous results using glucose analogs (1–3). We previously concluded the following reasons for this hypophagia. Glucose-sensitive neurons took up 1-DG by their glucose transport system (10–13). Then, 1-DG was phosphorylated by glucose hexokinase (14) and its phosphorylated forms were easily accumulated in the neurons (15). Probably, as in the case of 2-deoxy-D-glucose-6-phosphate (16, 17), intracellular accumulation of 1-DG-6-phosphate might cause ATP deficiency in the glucose-sensitive neurons in the lateral hypothalamus which leads to sustained inactivation of the Na^+ pump, and finally, excess Na^+ retention in the neurons that then results in decreased neural activity (3). It seems reasonable to consider that feeding suppression is induced by the DDG analogs in the same way, although the potency of the DDG analogs was less than that of 1-DG. Since these glucose analogs are considered to produce sustained inactivation after an initial increase of the glucose-sensitive neuron activity in the lateral hypothalamus (3), the prolongation of the

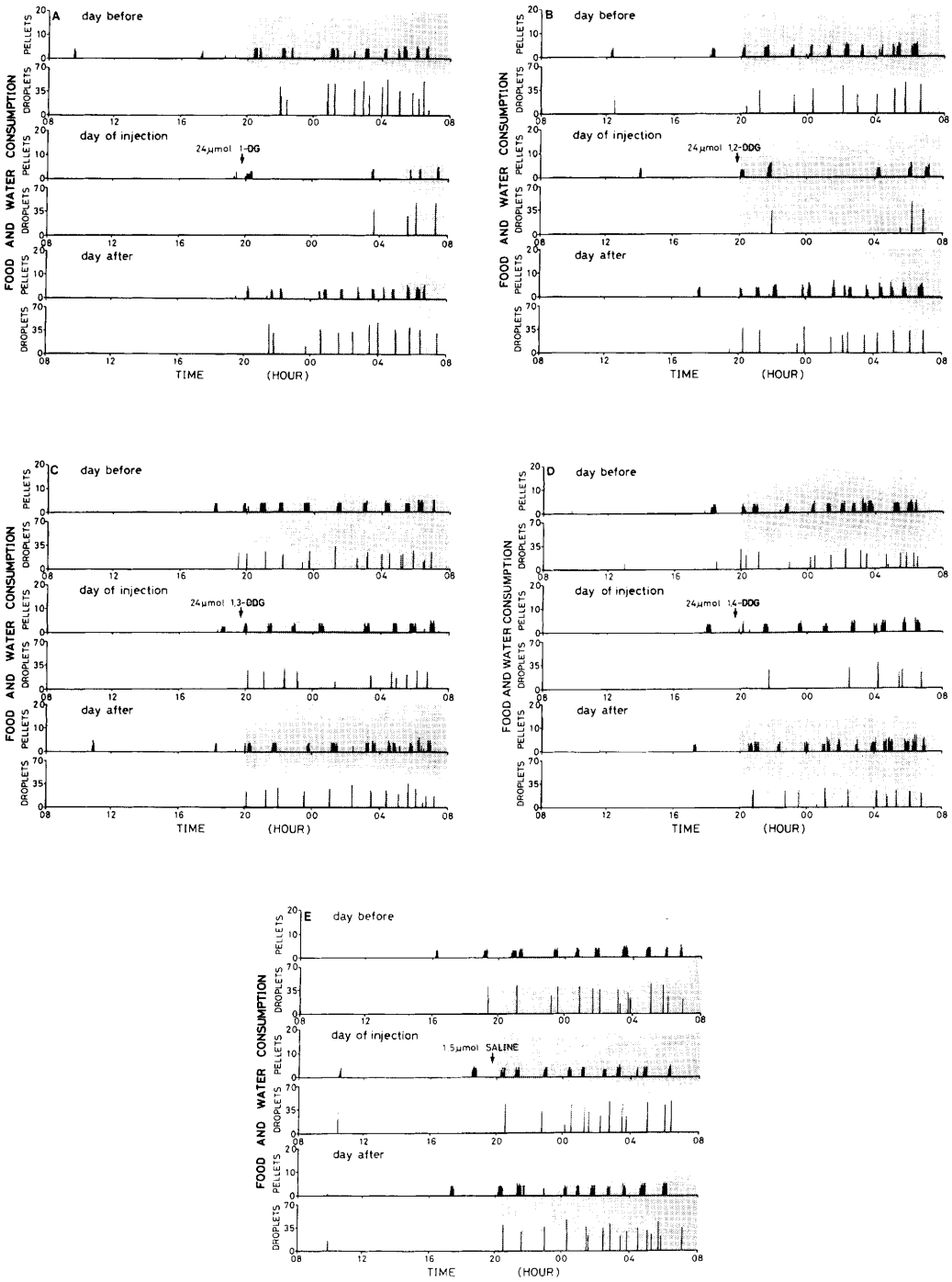

FIG. 2. Typical meal and drinking patterns during 36 hr before and 36 hr after infusion. In each daily record: upper vertical bars, cumulative number of standard pellets consumed per minute (mean weight of standard pellet: 48.2 ± 0.6 mg, ranging from 46 to 55 mg); lower vertical bars, cumulative number of water droplet consumed per minute (mean volume of droplet: 63.2 ± 0.9 μl, ranging from 56 to 70 μl); shaded, dark time. A: 24 μmole 1,5-anhydro-D-glucitol (1-deoxy-D-glucose); B: 24 μmole 1,2-dideoxy-D-glucose; C: 24 μmole 1,3-dideoxy-D-glucose; D: 24 μmole 1,4-dideoxy-D-glucose; E: 1.5 μmole saline.

postprandial intermeal interval induced by these analogs might be attributable to suppression of any eating burst that would be initiated by activation of the glucose-sensitive neurons (18).

Differences of anorectic actions between 1-DG and its DDG analogs seem to be a result of known differences in the biochemical modes of action in these analogs. First, phosphoglucose isomerase is known to have high substrate specificity only for glucose-6-phosphate and fructose-6-phosphate (15). In addition, a hydroxyl group at carbon 1 of these phosphates is essential for the binding of the substrate to this enzyme (15, 19, 20). A hydroxyl group at carbon 1 is also necessary for the binding of glucose-6-phosphate to glucose phosphate dehydrogenase (19). Together with these facts, phosphorylated forms of 1-DG and its analogs could not be substrates for phosphoglucose isomerase or glucose phosphate dehydrogenase under physiological conditions. For these reasons, the major differences in feeding behavior induced by 1-DG and its analogs probably do not appear at this step of glycolysis.

Second, 1-DG could be a substrate for the brain enzyme, hexokinase (14). However, lack of a hydroxyl group at carbon 6 of 6-deoxy-D-glucose (6-DG) might preclude phosphorylation of this glucose analog (14, 21). There is little doubt that 1,6-DDG, which also lacks a hydroxyl group at carbon 6, cannot be phosphorylated. The hydroxyl groups at carbons 2, 3, and 4 of the glucose molecule must not be essential for enzyme-substrate affinity since 2-deoxy-D-glucose (2-DG), 3-deoxy-D-glucose (3-DG), and 4-deoxy-D-glucose (4-DG) can be phosphorylated (14). The substrate affinity is, however, significantly reduced by removal of the hydroxyl group at carbon 3 or 4, although removal of the hydroxyl group at carbon 2 has little influence on the affinity (14). This strongly suggests that 1-DG and 1,2-DDG may be more efficiently phosphorylated by hexokinase than 1,3-DDG or 1,4-DDG.

Third, 1-DG can cross the barrier from blood to brain (22) and is actively and passively transported into cells (10–13). It is also known that 2-DG is more efficiently transported into cells than glucose or any of its other analogs (13, 22–24). In addition, 3-DG, 4-DG, and 6-DG are transported into cells, although they have less affinity for the glucose transport system than glucose or 2-DG (13, 20, 25, 26). These facts indicate that removal of a single hydroxyl group does not inhibit transport of glucose per se, but the magnitude of affinity with the glucose transport system depends on the position from which the hydroxyl group is removed.

The biochemical characteristics of these analogs seem to almost explain our experimental data that 1,2-DDG and 1-DG suppressed feeding more potently than 1,3-DDG or 1,4-DDG, and that 1,6-DDG did not suppress feeding. However, our result that 1-DG suppressed feeding more potently than 1,2-DDG indicates that the phenomenon may, in addition, depend on another factor. The reason for this result remains unclear at this time.

The main reason for failure of the epimers of 1-DG, 1-deoxymannose, 1-deoxyallose, and 1-deoxygalactose, to suppress feeding may be the fact that spatial hindering groups are introduced into these by epimerization at each carbon (21, 22). D-Mannose which possesses an epimerized hydroxyl group at carbon 2 of the glucose molecule had little affinity for the glucose transport system, compared to 2-DG which has a hydroxyl group removed at carbon 2 (13, 21, 22). D-Allose and D-galactose, forms of the glucose molecule epimerized at carbons 3 and 4, were only slightly transported compared to the 2 or 3 deoxy analogs (13). There was no difference in affinity for the substrate of the enzyme, glucose hexokinase, between epimerized forms of the glucose molecule (14). Thus, one reason why 1-deoxymannose, 1-deoxyallose and 1-deoxygalactose induced no anorectic effect seems to be the possibility that they are not transported enough into cells to produce anorexia.

In conclusion, it is clear that 1-DG and its analogs suppress feeding mainly by prolonging postprandial intermeal intervals, and that the position of the carbon in the pyranose ring of glucose from which a hydroxyl group is removed affects each analog's contribution to feeding behavior.

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