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HUNGER MOTIVATION IN GOLDTHIOGLUCOSE-TREATED AND GENETICALLY OBESE FEMALE MICE[1]

DEVENDRA SINGH,[2] JOHN R. LAKEY, AND MELANIE K. SANDERS
University of Texas at Austin

Genetically obese, goldthioglucose-injected, and control mice were compared for strength of hunger motivation as assessed by their performance on the following tasks: taste reactivity, readiness to eat, food-directed activity, and passive avoidance. On the basis of these tests, it appears that genetically obese mice have greater strength of hunger motivation than either goldthioglucose-injected or control mice, while goldthioglucose-injected and control mice exhibit similar strength of hunger motivation.

Quite a few studies have shown that rats with electrolytic lesions in the ventromedial hypothalamic (VMH) area become hyperphagic, exhibit finickiness (i.e., overreaction to taste and food adulteration), and perform more poorly than normal rats on hunger motivation tests. Furthermore, the degree of finickiness and magnitude of performance deficit on hunger and motivation tests are greater in such animals when they are in the static as compared with dynamic stage of the lesion effect (for review see Teitelbaum, 1961). On the basis of such findings it is commonly suggested that animals with VMH damage overeat but are less hungry than normal animals.

Hypothalamic hyperphagia similar to that of rats has been reported in other species such as mice, rabbits, cats, and monkeys; however, that hyperphagia is apparently not accompanied by any deficit in hunger motivation. For example, Balinska (1963) reported that dynamic hyperphagic rabbits pull a ring to obtain food significantly more often and much faster than normal rabbits. Likewise, Hamilton and Brobeck (1964) reported that dynamic hyperphagic monkeys obtain more pellets than normal monkeys on lower fixed-ratio schedules; when higher ratios are used, both hyperphagic and normal monkeys perform alike. These authors further report that when quinine-mixed food pellets were provided, all monkeys with VMH lesions ate as much as normal monkeys. These findings suggest that the deficit in hunger motivation observed in rats with VMH lesions may be a species-specific phenomenon.

To further explore this possibility, hunger motivation in mice with hypothalamic damage was investigated. It has been repeatedly shown that one intraperitoneal injection of goldthioglucose (GTG) causes extensive damage to the VMH area and produces hyperphagia and subsequent obesity in mice. Although GTG injections do produce damage to the kidney and the liver, changes in feeding behavior appear to result directly from the lesions in the brain (Leibelt & Perry, 1967). The regulation of feeding behavior of GTG-treated mice is quite similar to that of rats with VMH damage (for review see Liebelt and Perry, 1967; Ruiter, Wiepkema, & Reddingius, 1969; Wiepkema, 1968), although no information is available in regard to their strength of hunger motivation. The present experiments were conducted to investigate the strength of hunger motivation in mice made obese by GTG injection in a variety of situations, viz., taste responsivity, readiness to eat in a novel environment, effect of a work requirement to obtain food, and passive avoidance. All GTG-injected mice were tested when they became obese, since finickiness and deficit in hunger motivation in rats has been shown to be more pronounced during the static phase than during the dynamic phase of VMH lesions. Furthermore, since a few studies

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[2] Requests for reprints should be sent to Devendra Singh, University of Texas, Mezes Hall 316, Austin, Texas 78712.

(Fuller & Jacoby, 1955), have shown that genetically obese mice regulate their food intake in a fashion quite similar to GTG-treated mice, a group of genetically obese mice were also tested. The comparison between genetically obese mice and those made obese by GTG injection should enable one to ascertain whether the pronounced performance deficits observed during the static phase might be due to excessive body-fat deposits alone. Additionally, some recent studies (e.g., Nisbett, 1972; Schachter, 1971) have suggested that obesity per se, in otherwise normal animals, can produce many disorders similar to those found in VMH-lesioned rats. The comparison between genetically obese mice and those made obese by GTG injection should shed light on this issue.

General Method

Subjects

Female genetically obese mice (C57/BL/6J-Ob) and female (C57/BL6J) mice were used in all experiments. Subjects were individually housed and maintained on a 12-hr. light/dark cycle throughout the experimental condition. Food (Purina Rat Chow) was presented in a 1-in.-diam. cup, and water was presented in 100-ml. graduated bottles. Daily food and water intake was recorded for subjects throughout the experimental conditions. Spilled food was caught on a pan under the cage for later weighing. A bottle was hung on an empty cage to provide an estimate of spillage due to handling and evaporation.

Hypothalamic damage was produced in half of the normal subjects by one intraperitoneal injection of GTG. The dosage was .05 mg/gm body weight. The control subjects were given peanut oil injections as a placebo control. All subjects were maintained on ad-lib food and water for 3 mo. During this period, daily food and water intake and body weight were recorded on every tenth day. Table 1 shows mean body weight and daily food and water intake of goldthioglucose-treated (GTG), genetically obese (GOB), and control groups before the start of reported experiments.

Experiment 1: Taste Reactivity

The purpose of this experiment was to investigate the reaction of GTG-treated mice to sugar, saccharin, and quinine solutions. On the basis of hyperphagic rats' data, it was expected that GTG-treated mice would exhibit "finickiness" and consume more of sweet solutions and less of quinine solutions.

Method

Subjects. Subjects were 20 genetically obese, 15 GTG-treated, and 10 control mice.

Procedure. Taste reactivity was investigated by mixing either .25% saccharin sodium, 3% dextrose, or .12% quinine sulfate in regular tap water. Solutions were prepared fresh daily. The order of presentation of the different solutions was random, and each solution was presented for 4 consecutive days. In order to eliminate prior taste effects, all subjects were given plain tap water for 4 successive days between solutions. During this testing, all subjects were provided with ad-lib food, and the only liquid available was the test solution. Individual food and fluid consumption were recorded daily. Body weight was recorded every other day.

Results and Discussion

The main findings are depicted in Figure 1.

First, it should be noted that the GTG group drank the least amount of the plain tap water, while the GOB group drank the most. The food/water ratio under the tap water condition for the GTG group was 1.04 while for the GOB group the ratio was .63 and for the control group .66 (see Table 1). Thus, unlike GOB and control mice, GTG mice consumed less water and appeared to be hypodipsic. A similar hypodipsia has been reported in hypothalamic hyperphagic rats (Stevenson, 1969).

When 3% dextrose was presented, the GTG group drank significantly more of this solution compared to their intake of plain tap water (100% increase). The control group also drank slightly more of the dextrose solution. However, the intake of the GOB group was unaffected by mixing dextrose in their water, and they drank as much of this solution as of tap water. When .25% saccharin was presented, both GTG and control groups drank more than they had of the dextrose solution or plain tap water. Although the GTG group drank the most saccharin solution, group differences were not significant. Thus, it appears that GTG mice consume more sweet solution whether of dextrose or saccharin, while the intake of GOB mice is unaffected by this manipulation.

When the .12% quinine solution was presented, significant group differences in con-

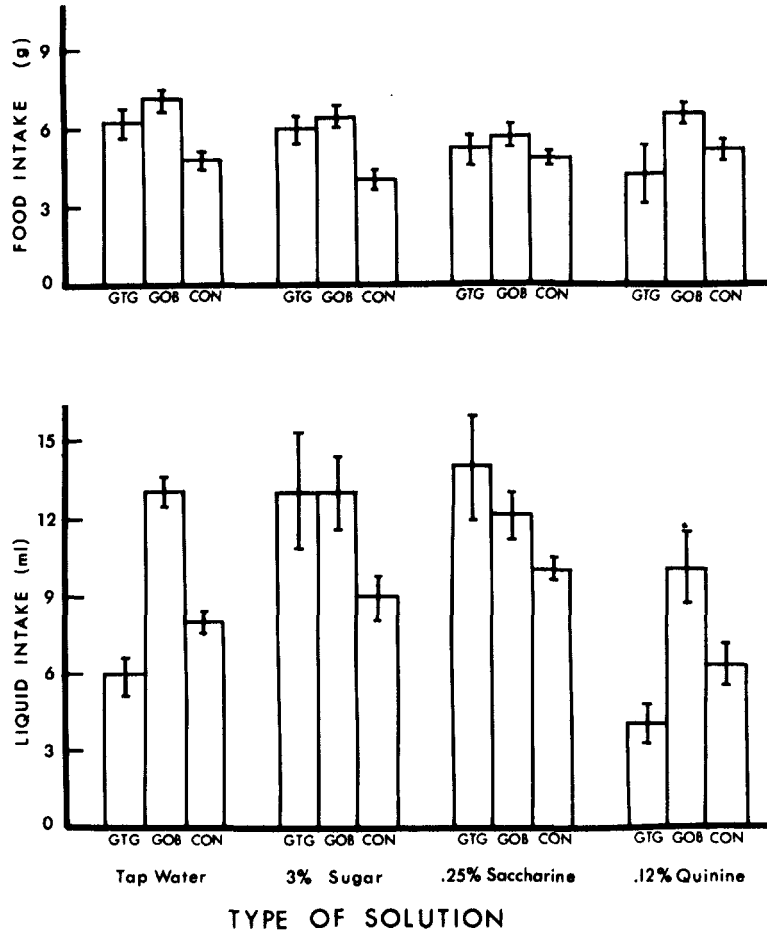

FIGURE 1. Mean daily liquid and food intake under different types of solution for genetically obese (GOB), goldthioglucose-injected (GTG), and control (CON) groups. (The vertical line in each bar diagram represents the standard error of the mean.)

sumption were evident ($F = 8.06$, $df = 2/35$, $p < .001$). The GOB group drank significantly more than either the GTG or control groups. The GTG group drank the least amount of water under this condition, although their intake was not significantly different from the control group. The reactivity of the GTG group to quinine is also evident in their food intake: Only with quinine solution did the GTG group consume less food than the control group. Finally, it should be pointed out that food/water ratios under different solutions were approximately identical for all three groups (see Figure 1). Thus, hypodipsia in GTG mice becomes evident only when they are maintained on plain tap water.

In summary, these data show a few similarities and differences between GTG mice and hypothalamic hyperphagic rats. Within the restraint of the present experimental design, GTG mice show reactivity to sweet solutions similar to that reported for hyperphagic rats. The reaction of GTG mice to quinine is similar but not as pronounced as that reported for hyperphagic rats. The intake of GOB mice is little affected by these adulterations, and surprisingly they do not react to quinine solution even to that degree shown by control mice. If tolerance to qui-

nine adulteration is taken as a measure of hunger motivation, then it appears that GOB mice were hungrier than the other two groups.

Experiment 2: Readiness to Eat

One of the simplest methods to infer the strength of hunger is readiness of an animal to eat in a novel situation (Bolles, 1962). Utilizing this test, Sclafani, Belluzzi and Grossman (1970) have shown that hyperphagic rats initiate eating significantly faster than normal rats. The present experiment attempted to investigate whether GTG-treated mice would react similarly.

Method

Subjects. Twenty genetically obese, 15 GTG-treated, and 10 control mice were tested. All these subjects were used in the first experiment and were maintained on ad-lib food and water for approximately 10 days before the start of the present experiment.

Apparatus. Four identical operant-conditioning boxes (12 × 12 × 12 in.) with a ¼-in. wire mesh floor and a hinged top were used. A metal feeder (1-in. diam.) was mounted on one side approximately ½-in. from the floor. A 15-w. white light bulb, mounted on the top, was the only source of illumination in the box. Three sides and the top of the box were opaque, while the front wall was transparent to allow a clear view of the subject.

Procedure. For testing, all subjects were deprived of food for 23 hr. Each subject was placed in the box for 10 min. with the feeder cup containing 10 food pellets (20 mg. Noyes). The time taken by each subject to start eating after being placed in the box (latency) was recorded. Each subject was removed from the box when it had consumed all the pellets; otherwise, the subject was removed at the end of the 10-min. period, and the total number of pellets consumed were recorded.

Results and Discussion

Due to large within-group variability, median latency scores were computed for each group. Analysis of the data (based on a median test) showed that the GOB group took significantly less time (78 sec.) than either the GTG or the control group ($p < .036$ for both comparisons). The latency scores for GTG group (170 sec.) and control group (235 sec.) were also significantly different ($p < .031$). All subjects ate within 10 min. and consumed all the pellets.

TABLE 1

Mean Body Weight and Daily Food and Water Intake of Genetically Obese, GTG-Treated, and Control Groups Prior to Start of Experiments

Group	Food intake (in gm.)	Water intake (in ml.)	Food/water ratio	Body weight (in gm.)
Genetically obese (n = 20)				
M	7.40	13.07	.63	60.30
SE_M	.44	.57	.04	1.07
GTG treated (n = 15)				
M	6.33	6.11	1.04	47.00
SE_M	.64	.72	.41	2.10
Control (n = 10)				
M	5.34	8.20	.66	24.10
SE_M	.27	.48	.07	.69

Note. All subjects were 160–180 days old at the start of the experiments. Abbreviation: GTG = goldthioglucose

Exploratory behavior of the different groups was quite in keeping with the respective latencies to feed. The GOB group explored the least and started eating soon after being placed in the box. The GTG group explored slightly more than the GOB group. The control groups explored the most. No instances of freezing were observed in either the GTG or GOB groups, while a few control mice did exhibit freezing. Inferring the strength of hunger motivation from these data, it appears that both GOB and GTG mice were hungrier than control mice.

On the basis of their shorter latencies and their reaction to quinine solution (Experiment 1), it would appear that GOB mice have greater hunger motivation than either GTG or control mice. The behavior of GTG mice was quite similar to that reported for hyperphagic rats (Sclafani et al., 1970); like hyperphagic rats, GTG mice took less time than control mice in initiating eating, suggesting that GTG mice have greater hunger motivation.

Experiment 3: Food-Directed Activity

Hyperphagic rats have been shown to reduce their food intake drastically when required to work for their food. For example,

Teitelbaum (1957) has shown that on successively increasing fixed-ratio (FR) schedules, hyperphagic rats eat significantly less than control rats. The present experiment employed successively increasing FR schedules identical to those reported by Teitelbaum (1957) to investigate whether GTG-treated mice would show an effect similar to that of hyperphagic rats in this situation.

Method

Subjects and apparatus. A total of 9 genetically obese, 9 GTG obese, and 7 control mice were used. All animals were previously employed in the first 2 experiments. The apparatus was the same as used for experiment 2 with the addition of a lever to activate the food-delivery mechanism. All FR schedules were programmed with digital electronic apparatus. The number of reinforcements (20-mg. Noyes pellets) and the number of responses for each subject were recorded on electromechanical counters.

Procedure. After initial bar-pressing training, all subjects were tested for 4 hr. on each of 20 successive days. All subjects were trained to an FR256 schedule by spending 4 days on each of the following FR schedules: 1, 4, 16, 64, and 256. All subjects were maintained at 80% of their ad-lib body weight. Water was freely available in the home cage.

Results and Discussion

The median number of responses (averaged over 4 days) made by each group under the different ratio schedules is shown in Figure 2. The number of responses made by the GTG group was higher than that for either the GOB or control group under FR1 and FR4, although performance differences among groups were not statistically significant. It should be pointed out that hyperphagic rats also perform slightly better than control rats on lower ratio schedules (Teitelbaum, 1957). The number of responses given by each group monotonically increases with higher ratios up to FR64; however, the groups performances become strikingly different and were quite unexpected under the FR256 schedule. On the basis of the reported performance of hyperphagic rats, it was anticipated that the GTG group would perform significantly more poorly than the control group on FR256. However, as is evident from Figure 2, both GTG and control groups performed approximately alike on FR256. The GTG and control groups gave less responses on FR256 compared to the number of responses given on FR64. The GOB group, however, gave more responses on FR256 than FR64 thus maintaining a monotonic function throughout all employed schedules. The performance difference between GOB and control groups on FR256 was statistically significant (median test, $p < .031$). Thus, these data suggest that GOB mice have greater motivational strength than both GTG and control mice, while GTG and control mice exhibit a similar degree of hunger motivation. As pointed out in the introduction, hyperphagic monkeys (Hamilton & Brobeck, 1964) and rabbits (Balinska, 1963) also do not exhibit any motivational deficit in food-directed activity on tests similar to the one employed in the present study. However, it should be pointed out that the lack of motivational deficit observed in hyperphagic animals in the present study could be due to the fact that all animals were tested under reduced body weight. It has been previously demonstrated that under certain training and testing conditions hyperphagic rats can be made to work as hard as normal rats to obtain food (Singh, 1973b).

Experiment 4: Passive Avoidance

This experiment was conducted to ascertain whether GTG-treated mice would exhibit a performance deficit similar to that reported for hyperphagic rats (e.g., Margules & Stein, 1969; Singh, 1973a) on a passive-avoidance test.

Method

Subjects and apparatus. Subjects were 8 GTG-injected, 7 genetically obese, and 8 control mice. All subjects were used in the previous 3 experiments. The apparatus used was a modified operant-conditioning chamber (12 × 12 × 12 in.) with a brass rod grid floor which could be electrified. The lever was retracted, and a 100-ml. graduate water bottle was attached. The apparatus was so programmed that, during testing, whenever the subject touched the metal nipple of the water bottle, a shock (.5 sec., .3 ma., 480 v.) was delivered to the floor grid.

Procedure. Initially, each subject was left in the apparatus for 30 min., and the water consumed during this period was recorded. The total daily water

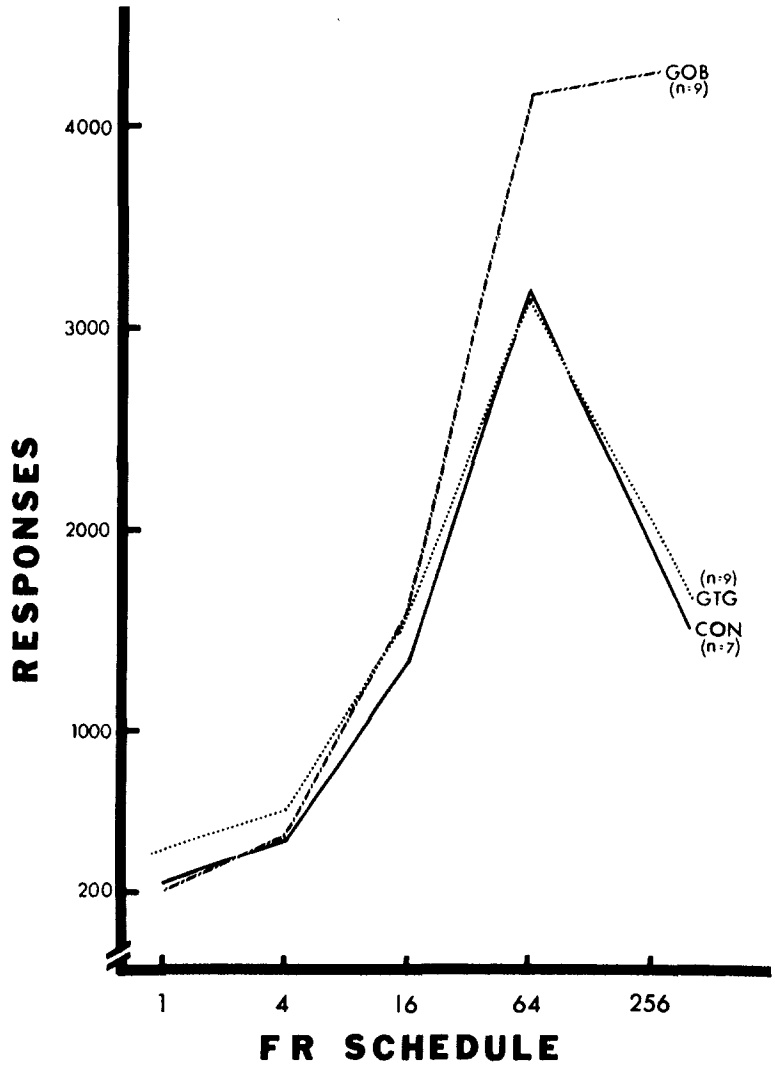

FIGURE 2. Median number of responses made by genetically obese (GOB), goldthioglucose-injected (GTG), and control (CON) groups at different ratio schedules.

intake of each subject was restricted to the amount consumed in the apparatus. After 4 consecutive days of this training, testing was started. The subject was permitted to drink water for 10 sec.; thereafter each contact with the nipple of the water bottle resulted in shock. After 15 min. in the apparatus, the subject was removed and provided with water for 30 min. in the home cage. The second day of testing was identical to the first day of testing except latencies (time interval between the placement in the apparatus and initiation of drinking) were recorded for all subjects. If a subject did not start drinking within 10 min. after being placed in the apparatus, the subject was not tested further. The number of shocks obtained during both days of testing was recorded for each subject.

Results and Discussion

The mean numbers of shocks obtained by the different groups were approximately identical on the first day of testing. On the average, GTG mice took 6 shocks, the GOB 5 shocks, and the controls 4 shocks; the differences were not statistically significant. In light of the fact that GTG mice were hypodipsic, it was quite surprising that they took almost as many shocks to obtain water as the GOB and control animals. The possibility that the performance of any group was

due to impaired learning ability can be ruled out on the basis of second day performance. All groups have approximately identical long latencies and took only about 1 shock during the testing session. Thus, unlike hyperphagic rats, GTG mice do not perform poorly on the passive-avoidance test.

General Discussion

The main purpose of these experiments was to investigate whether GTG-treated and genetically obese mice exhibit finickiness and deficits in hunger motivation similar to those reported for hypothalamic hyperphagic rats. Reliable differences between control and experimental mice were evident in taste responsiveness, readiness to eat, and food-directed activity. The goldthioglucose-treated mice drank slightly more of dextrose and saccharin solution and significantly less of quinine solution than control mice. The genetically obese mice did not exhibit marked reactivity and maintained an approximately similar intake of the different solutions. Thus, these data show that only goldthioglucose-treated mice exhibit overreactivity to taste similar to hyperphagic rats. Furthermore, if reaction to quinine solution, readiness to eat in a novel environment, the amount of food-directed activity, and performance on the passive-avoidance test are accepted as measures of motivational strength, then GTG-treated mice do not have any motivational deficit.

The idea that damage to the VMH area produces hyperphagia as well as lowered motivation is primarily based on the research done with rats. In other species such as monkeys (Hamilton & Brobeck, 1964) and rabbits (Balinska, 1963) hypothalamic hyperphagia is not accompanied by any deficit in hunger motivation. There is also some evidence suggesting that even in hyperphagic rats lower hunger motivation can be demonstrated only under certain training and testing conditions. For example, Singh (1973b) has shown that extensive preoperative training on a food-motivated task obliterates performance differences between hypothalamic hyperphagic and normal rats. Furthermore, even in a situation where food can be freely obtained or where it can be obtained only by pressing a bar, hyperphagic rats prefer—like normal rats—to obtain most of their food by bar pressing (Singh, 1972). On the basis of these findings it appears that the notion that VMH damage produces a deficit in hunger motivation may be true only for rats in some highly specific situations.

This investigation is also addressed to the issue of whether some of the reported behavioral deficits in obese hyperphagic animals could be due to body fat deposit alone. This speculation would have been supported if genetically obese mice had behaved in a manner similar to that of mice made obese by goldthioglucose injection. However, genetically obese mice and goldthioglucose-injected mice differ from each other in several important ways. First, it seems that genetically obese mice were more hungry than goldthioglucose-injected mice. This is inferred from readiness to eat data and the amount of food-directed activity. Furthermore, genetically obese mice exhibited no hypodipsia when plain tap water was presented. They also were not overreactive to the taste properties of the different solutions. Unlike goldthioglucose-injected mice, their liquid intake was more or less unaffected by adulteration.

These findings do not confirm previous reports that genetically obese mice overreact to sweet and bitter tastes. Some procedural differences between the studies could probably explain this disparity. Fuller and Jacoby (1955) used male mice and mixed quinine in food while in the present study female mice were used and quinine was mixed in drinking water. Also, Fuller and Jacoby used a larger quantity of quinine (.24%) than that used in the present study (.12%). It is quite possible that genetically obese mice would have overreacted to quinine at higher concentrations and/or when mixed with food.

REFERENCES

Balinska, H. Food preference and conditioned reflex type II activity in dynamic hyperphagic rabbits. *Acta Biologiae Experimentalis,* 1963, **23,** 33-44.

Bolles, R. C. The readiness to eat and drink: The effect of deprivation conditions. *Journal of*

Comparative and Physiological Psychology, 1962, **55,** 230–234.

FULLER, J. L., & JACOBY, G. A. Central and sensory control of food intake in genetically obese mice. *American Journal of Physiology,* 1955, **183,** 279–283.

HAMILTON, C. L., & BROBECK, J. R. Hypothalamic hyperphagia in the monkey. *Journal of Comparative and Physiological Psychology,* 1964, **57,** 271–278.

LIEBELT, R. A., & PERRY, J. H. Action of goldthioglucose on the central nervous system. In C. F. Code (Ed.), *Handbook of physiology.* Sec. 6. Vol. 1. Washington, D. C.: American Physiological Society, 1967.

MARGULES, D. L., & STEIN, L. Cholinergic synapses in the ventromedial hypothalamus for the suppression of operant behavior by punishment and satiety. *Journal of Comparative and Physiological Psychology,* 1969, **67,** 327–335.

NISBETT, R. E. Hunger, obesity, and the ventromedial hypothalamus. *Psychological Review,* 1972, **79,** 433–453.

RUITER, L. DE, WIEPKEMA, P. R., & REDDINGIUS, J. Ethological and neurological aspects of the regulation of food intake. *Annals of the New York Academy of Sciences,* 1969, **157,** 1204–1214.

SCHACHTER, S. Some extraordinary facts about obese humans and rats. *American Psychologist,* 1971, **26,** 129–144.

SCLAFANI, A., BELLUZZI, J. D., & GROSSMAN, S. P. Effects of lesions in the hypothalamus and amygdala on feeding behavior in the rat. *Journal of Comparative and Physiological Psychology,* 1970, **72,** 394–403.

SINGH, D. Preference for mode of obtaining reinforcement in rats with lesions in septal or ventromedial hypothalamic area. *Journal of Comparative and Physiological Psychology,* 1972, **80,** 259–268.

SINGH, D. Comparison of behavior deficits caused by lesions in septal and ventromedial hypothalamic areas in the female rat. *Journal of Comparative and Physiological Psychology,* 1973, **84,** 370–379. (a)

SINGH, D. Effects of preoperative training on food-motivated behavior of hypothalamic hyperphagic rats. *Journal of Comparative and Physiological Psychology,* 1973, **84,** 47–52. (b)

STEVENSON, J. A. F. Neural control of food and water intake. In W. Haymaker, E. Anderson, & W. J. H. Nauta (Eds.), *The hypothalamus.* Springfield, Ill.: Charles C Thomas, 1969.

TEITELBAUM, P. Random and food-directed activity in hyperphagic and normal rats. *Journal of Comparative and Physiological Psychology,* 1957, **50,** 486–490.

TEITELBAUM, P. Disturbances in feeding and drinking after hypothalamic lesions. In M. R. Jones (Ed.), *Nebraska Symposium on Motivation: 1961.* Lincoln: University of Nebraska Press, 1961.

WIEPKEMA, P. R. Behaviour changes in CBA mice as a result of one goldthioglucose injection. *Behaviour,* 1968, **32,** 179–210.

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