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Sex differences in hyperphagia and body weight gains following goldthioglucose-induced hypothalamic lesions in mice*

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Hypothalamic damage was induced in age-matched male and female albino mice by goldthioglucose injection, and their food consumption and body weight were compared over the following 60-day period. Sex differences in food consumption were also investigated as a function of palatability of food. Results show no significant sex differences in food consumption, although marked sex differences in body weight gain were noted. Female mice with hypothalamic damage gained more body weight than did male mice with hypothalamic damage. These results suggest that obesity induced by hypothalamic damage is probably due to the combined effects of neural and hormonal changes.

Hyperphagia induced by damage to the ventromedial hypothalamus (VMH) has been extensively studied in rats and mice. In rats, the VMH area is most frequently destroyed by the electrolytic lesioning method, while in mice, intraperitoneal injection of goldthioglucose (GTG) is extensively used to produce VMH damage. Although GTG injections do injure the liver and kidney, changes in feeding behavior appear to result directly from the VMH damage (Liebelt & Perry, 1967). In spite of such differences in lesion techniques, both rats and mice exhibit remarkably identical behavior deficits: a period of hyperphagia accompanied by finickiness (i.e., overreaction to taste and food adulteration) and subsequent obesity (Teitelbaum, 1961; Liebelt & Perry, 1967; Weipkema, 1968).

Interest accrued in this laboratory as to whether other parallels existed between VMH electrolytically lesioned rats and GTG-injected mice. For example, recent studies (Singh & Meyer, 1968; Valenstein, Cox, & Kakolewski, 1969) have shown greater food consumption and body weight gains following VMH electrolytic lesions in female as compared to male rats. Singh (1970) replicated these findings; however, he observed no sex difference in regard to food preferences. If similar sex differences can be demonstrated in mice, it would extend and add to the reliability of the reported behavioral congruence between VMH-damaged rats and mice. Therefore, the present experiment examines sex differences in weight gains and finickiness in GTG-injected mice.

METHOD

Subjects

The Ss were 70 (35 male and 35 female) inbred Swiss albino mice (supplied by the Charles River Company), 100 days of age at the start of the experiment. All Ss were housed in individual wire mesh cages and were maintained on a 12-h light-dark cycle throughout the experiment. Food was placed in hoppers attached to the outside of cages, and spilled food was caught on wax paper placed under the cage. Water was provided in 100-ml graduated bottles.

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Pre- and Postinjection Procedure

All Ss were provided with ad lib regular food (Purina Rat Chow) and tap water for 10 days before injection. Daily food and water consumption and body weigh were recorded. At the end of this period, all Ss were deprived of food for 24 h to receive (intraperitoneally) either peanut oil based goldthioglucose (supplied by Schering Corporation) or a peanut oil placebo. The goldthioglucose dose for both male and female animals was 0.5 mg/g body weight. Sixteen injected animals (9 females and 7 males) died during the course of the experiment; therefore, the reported results are based on 22 control (11 male, 11 female) and 32 injected (14 male, 18 female) animals.

Twenty-four hours after injection, all animals were given ad lib regular food and water for 10 consecutive days. The "finickiness" tests were started on the 11th postinjection day. In addition to regular food (Purina Rat Chow), three different types of food (prepared by mixing saccharin sodium, quinine sulfate, or cellulose by weight in the regular food) were used: 0.14% saccharin-mixed, 12.5% cellulose-mixed, and 0.13% quinine-mixed. All four types of food were presented in solid pellet form. The sequence of presentation, except for regular food, was determined randomly. Each type of food was presented for 4 consecutive days with intervening 4-day periods during which the Ss were given regular food. All animals were given ad lib food and water for each type of food. At the end of the "finickiness" tests, all animals were maintained on regular food until the 70th postinjection day. Daily records of food and water consumption and body weight were continued throughout postinjection testing.

On the 71st postinjection day, all animals were sacrificed and their brains removed. These were embedded in paraffin, sectioned at 6 microns, and stained in Hemotocylin and Eosin (H&E). The brains were then reconstructed to determine the locus and extent of damage.

RESULTS

Histological Observation

First of all, it should be stressed that GTG-induced brain damage was approximately identical for both

Table 1
Daily Food Consumption by GTG-Injected and Control Ss as a Function of Type of Food

Group		Type of Food				
		*Regular	Saccharin-Mixed	Cellulose-Mixed	Quinine-Mixed	Regular†
				GTG-Injected		
Male (N = 14)	Mean	5.7	5.5	5.8	4.2	4.9
	SD	1.3	1.8	1.6	0.9	1.4
Female (N = 18)	Mean	5.8	5.2	5.7	3.8	4.1
	SD	2.3	1.5	1.9	1.0	1.0
				Control		
Male (N = 11)	Mean	4.0	4.5	5.9	4.1	4.3
	SD	0.7	1.1	1.3	1.1	1.2
Female (N = 11)	Mean	3.5	4.2	5.3	3.6	3.8
	SD	0.8	1.3	1.0	1.4	1.0

Note–The order of presentation for different types of food was saccharin, cellulose, and quinine. All animals obtained 4 days of regular food before being switched to the next type of food.
**Based on postinjection Days 3-10.* *†Based on 4 consecutive days starting on 67th postinjection day.*

male and female animals. All Ss had extensive damage in the hypothalamus and some damage to extrahypothalamic structures (septum and hippocampus). As expected on the basis of previous findings (Leibelt & Perry, 1967), the main spread of lesions in the hypothalamus was in the anterioposteral and dorsoventral direction rather than in the lateral direction. The most extensive damage was in the infundibular region; in a large number of cases, the area surrounding the VMH, third ventricle, and arcuate nucleus was bilaterally damaged. The anterior-posterior extent of damage was between mammillary bodies and optic chiasma.

It should be pointed out that the Ss which gained the most body weight, regardless of sex, revealed extensive damage spreading from VMH to the arcuate nucleus. The S gaining least amount of body weight had less damage in VMH and more damage ventrally. No significant relationship between extent of damage and extent of "finickiness" was evident for either sex.

General Behavior

GTG-injected Ss appeared to be less active in their cages than control Ss throughout the duration of the experiment. Another striking behavioral difference between GTG-injected and control animals was that during the time of daily food and water measurement, none of the GTG-injected animals were found climbing on the wire mesh front of the cage; before injection, almost all of the animals climbed the wire mesh front. A similar decrease in climbing behavior after GTG injection has been reported by Wiepkema (1968). Finally, no changes in emotionality (as inferred from biting, struggling, and vocalization when picked up) was evident in either control or GTG-injected animals. It should be pointed out that rats with VMH damage are reported to be hyperemotional (Singh, 1969).

Food Intake

For the first 3 days following injection, practically all GTG-injected animals ate 2 g or less food; therefore, the data for the first 3 days have been excluded from 10 days of regular food testing. The daily mean food consumption under different types of food is presented in Table 1.

First of all, it should be noted that normally male mice eat slightly more food than do female mice of comparable age. This is evident from Table 1, which shows that control male animals ate slightly more than control female animals for all types of food.

Both GTG-injected males ($t = 3.8$, $df = 24$, $p < .01$) as well as females ($t = 4.1$, $df = 23$, $p < .01$) ate significantly more than their respective control groups when regular food was provided (Postinjection Days 3-10). Although both male and female GTG-injected groups ate approximately equal amounts of regular food, female GTG groups represent an increase of 65%, while male GTG groups showed an increase of 42% over their respective control groups. When saccharin-mixed food was presented, both GTG-injected males ($t = 5.6$, $df = 24$, $p < .01$) and females ($t = 3.9$, $df = 28$, $p < .01$) ate significantly more than their controls. However, surprisingly, both male and female GTG-injected groups ate slightly less amounts of saccharin than regular food. This finding is puzzling, since it was expected that GTG-injected Ss would exhibit greater reactivity to taste. Likewise, the food consumption when cellulose-mixed food was presented was quite unexpected. On the basis of previous findings with VMH-lesioned rats, it was expected that the GTG-injected groups would eat less cellulose-mixed food than the control group. However, males and females in the GTG-injected group ate approximately the same amount of food as did control groups when cellulose-mixed food was available. The

Table 2
Sex Differences in Body Weight Gained by GTG-Injected and Control Ss

	Preinjection	Successive 5-Day Blocks													
		1	2	3	4	5	6	7	8	9	10	11	12	13	14
							GTG-Injected Female (N = 18)								
Mean	26.0	24.6	26.8	31.0	34.4	36.1	38.3	39.2	39.5	39.3	39.7	39.8	40.4	40.6	41.5
SD	3.1	3.5	3.6	5.6	6.6	6.7	8.3	9.6	10.3	11.6	12.2	13.1	13.6	13.4	12.8
							Control Female (N = 11)								
Mean	26.9	27.8	29.0	29.2	28.9	28.9	29.6	29.7	29.5	29.8	29.7	29.7	29.6	30.7	31.0
SD	2.5	2.7	3.0	2.8	2.5	2.8	2.9	2.5	2.4	2.1	2.2	2.3	2.1	2.2	2.3
							Injected Male (N = 14)								
Mean	35.4	34.8	29.5	29.5	41.2	40.6	41.1	40.7	41.8	41.8	42.1	42.3	42.8	43.3	43.7
SD	2.5	2.8	2.8	2.4	3.0	3.9	5.0	4.9	4.6	6.8	8.7	8.1	8.2	10.3	9.8
							Control Male (N = 11)								
Mean	37.1	38.2	39.7	39.8	40.0	39.6	39.6	39.4	40.0	40.0	39.6	39.5	39.7	40.7	41.6
SD	1.9	2.9	3.2	2.8	2.6	2.7	2.9	2.7	2.6	2.5	2.5	2.7	2.4	2.6	2.8

control group ate more cellulose-mixed food than regular food. The GTG-injected group, on the other hand, ate approximately the same amount of these two types of food.

When quinine-mixed food was present, all groups ate approximately the same amount. However, while the control groups ate approximately the same amount of quinine-mixed food as when regular food was available, the GTG-injected groups ate significantly less quinine-mixed compared to regular food (males: $t = 2.5$, $df = 27$, $p < .05$; females: $t = 5.8$, $df = 35$, $p < .01$). The female GTG-injected group ate 34% less quinine-mixed food than regular food, while the male GTG-injected group ate 26% less, although these differences were not statistically significant.

Table 1 also presents mean food consumption of regular food by the different groups when GTG-injected mice became obese (Postinjection Days 67-70). As is evident from Table 1, both male and female GTG-injected mice ate less food compared to their respective intakes during the dynamic phase (Postinjection Days 3-10). As a matter of fact, the food intake of GTG-injected mice was similar to that of the control groups. These results replicate the previous findings that the food-intake of GTG-injected mice becomes normal during the static phase (Wiepkema, 1968).

Finally, no sex differences were evident in daily water consumption under any type of food. Although GTG-injected animals drank more water than did control animals, this increase was mainly due to increased food consumption, since the food/water ratios for GTG-injected and control animals were approximately identical. Leibelt and Perry (1967) have also reported a lack of polydipsia following GTG injection.

Body Weight

Table 2 presents mean body weights for successive 5-day blocks for all groups. As is evident from Table 2, both GTG-injected male and female groups gained more weight than did their respective controls, though the magnitude of difference was greater for the female than for the male GTG-injected groups. The GTG-injected females gained, on the average, 10.5 g more than their controls, while GTG-injected males gained only 2.1 g more than their controls. A similar trend became evident when Ss gaining least and most body weight were compared. The female S that gained most weight gained 19 g more than the male S that gained most weight. This difference becomes more striking considering the fact that before injection the female was 4 g lighter than the male. Comparing the Ss that gained the least weight after injection, the female gaining the least weight was approximately of the same weight as the male, in spite of a lower initial weight.

DISCUSSION

The present findings show that GTG injection produces hyperphagia which is quite similar to that produced by electrolytic damage of VMH in rats. However, unlike rats with VMH damage, GTG-injected mice show much less "finickiness." GTG-injected and control animals eat approximately equal amounts of adulterated food, but not of the regular unadulterated food. It is quite possible that if greater amounts of saccharin, quinine, and cellulose were used, GTG-injected animals might have shown more pronounced "finickiness."

The obtained results also show that sex differences in obesity caused by GTG injection are similar to those reported for rats with VMH lesions (Singh & Meyer, 1968; Valenstein et al, 1969). The fact that GTG-induced hypothalamic damage produced similar sex differences in obesity to those observed after electrolytic lesioning of the VMH area in rats adds a great deal of generality and reliability to the reported role of sex differences in body weight regulation.

The mechanism responsible for the sex differences in

obesity after hypothalamic damage is not clear. The role played by gonadal hormones in food consumption and body weight regulation in normal rats has been demonstrated recently (Zucker, 1969). Thus, it is possible, as suggested by Valenstein et al, that obesity induced by hypothalamic damage is probably due to a combined effect of neural damage and hormonal change. This suggestion is quite consistent with the observation that VMH lesions in rats frequently produce gonadal atrophy (Valenstein et al, 1969) and with the observation that GTG injections in mice cause changes in the endocrine function (Leibelt & Perry, 1967). This, along with the fact that gonadectomy results in greater weight gains in females but decreased weight gains in males (Kakolewski, Cox, & Valenstein, 1968), provides a possible explanation for the differential weight gains shown by male and female Ss after hypothalamic damage.

Finally, it should be pointed out that apparently, under certain dietary conditions, marked sex differences in obesity after hypothalamic damage may not be evident. For example, Gold (1970) has shown that if female rats are equated for body weight with male rats and if both are maintained on high-fat diets after VMH lesions (produced surgically), then no sex differences in body weight gain become evident. It is possible that GTG mice would react similarly in certain dietary conditions. If so, this would lead to the puzzling conclusion that sex differences produced by VMH damage become evident only when Ss are maintained on a regular laboratory chow diet.

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