Physiological Psychology
1973, Vol. 1, No. 4, 337-340

Effects of thyroxine, propylthiouracil, and diet on basomedial hypothalamically lesioned rats

MILAN REZEK* and DENNIS A. VANDERWEELE†
University of California at Los Angeles, Los Angeles, California 90024

Male albino rats (half with basomedial hypothalamic lesions) were maintained on liquid food. Subgroups were treated with control handling, 15 or 150 micrograms thyroxine, or 5 mg of propylthiouracil intraperitoneally, daily for 16 days. In intact animals, liquid food yielded small weight gains. Also, thyroxine treatment stimulated adrenal enlargement, increased food intake, but produced lower weight gain, while propylthiouracil had no significant effect on food intake or body weight. Lesioned animals showed severe inanition on liquid diets despite avid consumption, and this starvation was potentiated by thyroxine administration. Only propylthiouracil treatment allowed weight gain in lesioned animals. This suggests a metabolic dysfunction following hypothalamic lesions which participates in the development of obesity.

The role of the hypothalamus in eating has been well substantiated since Hetherington and Ranson (1940) reported that lesions of the ventromedial portions produced obese animals. Hyperphagia and resultant obesity were characterized as a two-stage phenomenon: a dynamic phase during which the animal overeats and gains weight rapidly and a static phase during which the animal eats only enough to maintain the new increased weight (Brobeck, Tepperman, & Long, 1943). Miller (1964) pointed out, however, that overeating was not representative of an increased motivation for food and postulated that the ventromedial hypothalamus (VMH) served as a satiety area in food intake. One aspect of this syndrome, however, remains largely unstudied, that is, the temporal aspects of neuroendocrine involvement in hypothalamic obesity.

The dynamic phase of hypothalamic obesity, marked postoperative increases in eating, appears to occur too rapidly to be attributed to humoral agents (Brobeck, 1946). Lesions in the basomedial hypothalamus, however, may physically block endocrine releasing factor (RF) paths to the pituitary. Also, glandular changes secondary to the overeating following lesion, such as thyroid metabolic related changes, may participate in the development of obesity. The basomedial hypothalamic lesion might also directly destroy the site of production of various RFs as well as interfere with the efferent pathways to the pituitary. Reichlin (1966) found that lesions of the anterior basomedial hypothalamus, following hemithyroidectomy, inhibited the compensatory hypertrophy of the remaining lobe and hypothesized that TSH-RF stimulation was disrupted. Also, Schmid and Gonzalo (1956) had observed disturbances in ACTH secretion after lesions of the nuclei ventromedialis and dorsomedialis of the hypothalamus. These studies represent only a few illustrations of the disruption of endocrine function following hypothalamic lesions.

This experiment will attempt to evaluate some of the endocrine aspects involved in the dynamic phase of hypothalamic obesity. The concern is with the development of animals with basomedial hypothalamic lesions maintained on liquid diets and their postoperative changes in endocrine gland size and histology. The hypothesis postulates endocrine-regulated metabolic changes resultant from neural damage which actively promotes and maintains obesity in hypothalamic hyperphagia.

*Partially supported by Grant NS 7687-05 to Don Novin.
†Supported by NIMH Training Grant MH 06415 to the Brain Research Institute, UCLA, Los Angeles, California.

METHOD

Subjects

Fifty-three male albino Wistar rats—mean body weight of 120 g—were used. Twenty-six animals (Group B) received basomedial hypothalamic lesions, while the remaining animals were intact (Group A). The groups were further subdivided receiving either injections of 15 or 150 micrograms of Sigma brand sodium-L-thyroxine, 5 mg of Sigma brand propylthiouracil (PTU), or control handling daily. Table 1 gives the number of Ss in each subgroup and the procedural design.

Procedure

Animals were maintained on liquid diets, except as noted below, in cages 8 x 10 in. The liquid diet used was concentrated milk—brand name Enfalag—in an equal volume of distilled water with the following constituents: 3% protein, 7.5% fats, 14% carbohydrates, 0.71% minerals and vitamins. Milk was measured daily, and new portions were introduced in sterile bottles only. Water was ad lib throughout the experiment. All Ss were allowed 1 day of adaptation to the liquid diet before the drug treatments began, the fifth day postoperative for Group B Ss.

Group B Ss were operated under Equi-Thesin anesthesia (0.35 ml/100 g body weight). Bilaterally symmetrical electrolytic lesions were produced by direct current of 2.5 mA for 10 sec using conventional stereotaxic procedures. The animals were allowed 4 days postoperative on solid food and showed only a 20% mortality rate.

Drug treatments lasted for 16 days. Thyroxine pH ranged from 7.8 to 8.2 while PTU was prepared with 0.5 N NaOH and 0.5 N HCl to maintain its pH between 8.0 and 8.4. Both drugs were administered daily, intraperitoneally, in a volume of 0.5 ml

Table 1
Procedural Outline for All Subjects

	Intact Animals				Operated Animals			
Group	AT	ATT	APTU	AC	BT	BTT	BPTU	BC
N	6	6	6	6	6	6	7	3
Drug Treatment	No Lesion 15 μg thyrox daily	No Lesion 150 μg thyrox daily	No Lesion 5 mg PTU daily	No Lesion No Drugs	Lesion 15 μg thyrox daily	Lesion 150 μg thyrox daily	Lesion 5 mg PTU daily	Lesion No Drugs
	Three animals also maintained on solid food with no drug treatment and no lesion.				Four animals lesioned and maintained on solid food with no drug treatment			

saline. Control groups–BC and AC–received handling daily for amounts of time comparable to injected Ss.

Finally, seven animals were maintained at all times on solid food without any drug treatment. Four of these animals received basomedial hypothalamic lesions as in Group B Ss. These animals served as controls for glandular size and histology, body weight gain, and food intakes in the lesioned Ss, while the remaining Ss served as comparisons for Group A Ss. Animals on solid food are treated separately in the results.

Histology

At the end of the experimental period, thyroid and adrenal glands were dissected out prior to perfusion of the Ss with 10% Formol saline. Extent of the lesions was verified following cresyl violet staining. Thyroid and adrenal glands were weighed on a microbalance, fixed in Bouin's solution, and washed in 70% alcohol. Glands were later embedded in 10% gelatin for frozen sectioning at 20 (adrenal) or 30 (thyroid) microns and stained using hematoxylin-eosin.

RESULTS

Group A: Intact Animals

Glands

In untreated Ss on liquid food–Group AC–the thyroid and adrenal glands did not show any deviations from normal histology. On the other hand, exogenous thyroxine, Groups AT and ATT, was a potent stimulator of adrenal enlargement characterized by a widening of zona glomerulosa and an increased number of cells in the zona fasiculata. Also, thyroid gland histology revealed a markedly increased colloid content with mean glandular weights significantly lower in Group ATT Ss than in Group AC ($t = 3.3$, $p < .01$). PTU-treated Ss (Group APTU) showed enlarged columnar cells in the thyroid, and thyroid weight was significantly greater than in Group AC ($t = 4.6$, $p < .01$). The glandular picture for APTU Ss was one of increased activation, but PTU was blocking thyroxine utilization, producing the systemic picture of hypothyroidism and behavioral lethargy. Figure 1 shows the glandular weights and reciprocity existing between thyroid and adrenal glands in the intact animal.

Group B: Lesioned Animals

The location of the lesions was found to include parts of the caudal VMH, the arcuate nucleus, and parts of the median eminence. Most lesions were centered in the anterior portions of the basomedial complex. Only animals with extensive damage in the caudal VMH were included in these results.

Glands

Group BPTU Ss alone escaped the adrenal enlargement found in lesioned Ss on liquid food, indicant of the stress of inanition. As in intact animals, thyroxine treatment in animals with basomedial hypothalamic lesions produced colloid goiter and decreased thyroid weight–Groups BT and BTT had significantly lower thyroid weights than Group BC ($t = 3.7$, $p < .05$). Group BPTU animals' thyroid weights did not differ from controls'; gland weights for all Ss appear in Fig. 1.

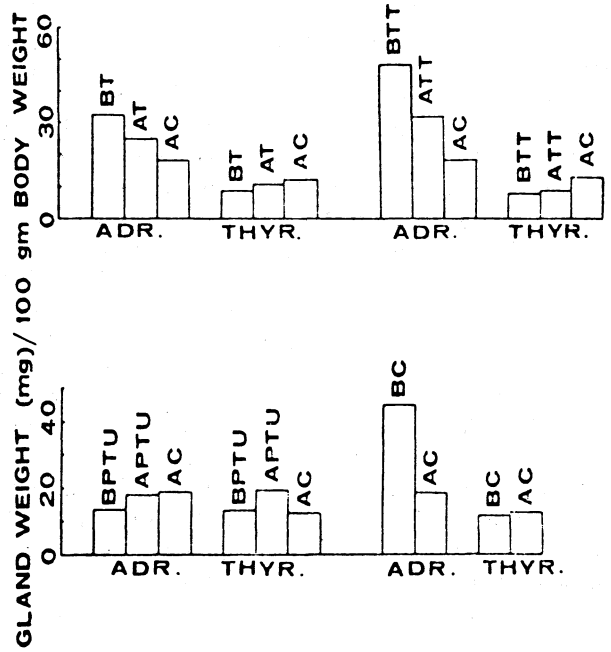

Fig. 1. Mean glandular weights of the adrenal and thyroid glands for all Ss. Note that Group AC appears in all four portions of the figure for comparison.

Food Intake and Weight Gain

Food intake differed significantly as a function of both lesions and drug treatment as shown by analysis of variance. A second analysis of variance demonstrated that weight gain was significantly affected by drug treatment, and while the main effect of operations (basomedial hypothalamic lesions) on weight gain was not significant, the interaction of Drug Treatments by Operations was significant. Both analyses of variance are summarized in Table 2.

Closer analysis of the groups reveals the following important differences. Food intake of intact, thyroxine-treated Ss was higher than that of Group AC and APTU animals ($p < .05$); weight gain, however, was only half that of untreated animals. Figure 2 graphs the weight gain as a function of the food ingested over the experimental period for each group; therefore, groups with Ss eating more food will show data points to the right of the graph, while groups with Ss eating smaller amounts of food will show data points more to the left of the graph. Also, groups showing more average weight gain per S will show data points more to the top of the graph than will groups where Ss gain less average weight. The slope of the line gives a picture of the efficiency of food utilization—the steeper the slope, the more weight gain being produced by the food consumed. Thyroxine-treated Ss, as shown by Fig. 2, are overconsuming but gaining little weight due to the increased metabolic rate produced by thyroxine. PTU-treated Ss eat less food but gain weight.

Comparisons of lesioned animals to their intact, similarly treated controls demonstrated that the lesioned Ss consistently eat *more* food but *lose* weight. The only lesioned Ss showing weight gain were the animals that were treated with PTU—Group BPTU. Group BC animals ate more food than intact controls and lost weight markedly. Thyroxine-treated Ss with basomedial hypothalamic lesions ate more than similarly treated, unlesioned animals and, again, lost weight. Indeed, some animals in Groups BC and BTT died of weight loss

Table 2
Summary Tables of Analyses of Variance on Food Intakes and Weight Gains as a Function of Basomedial Hypothalamic Lesions and Drug Treatments

Source	SS	df	MS	F
Food Intake				
Operations	373.19	1	373.19	12.71*
Drug Treat.	930.22	3	310.07	10.56*
A by B	35.15	3	11.71	
Error		38	29.36	
Weight Gain				
Operations	99.81	1	99.81	3.26
Drug Treat.	7197.08	4	1799.24	58.78*
A by B	829.51	4	207.22	6.77*
Error		46	30.61	

Note—The dfs are not the same for food intake and weight gain analyses of variance as the results of the control animals on solid food are not comparable to liquid food animals when considering amounts of food ingested.

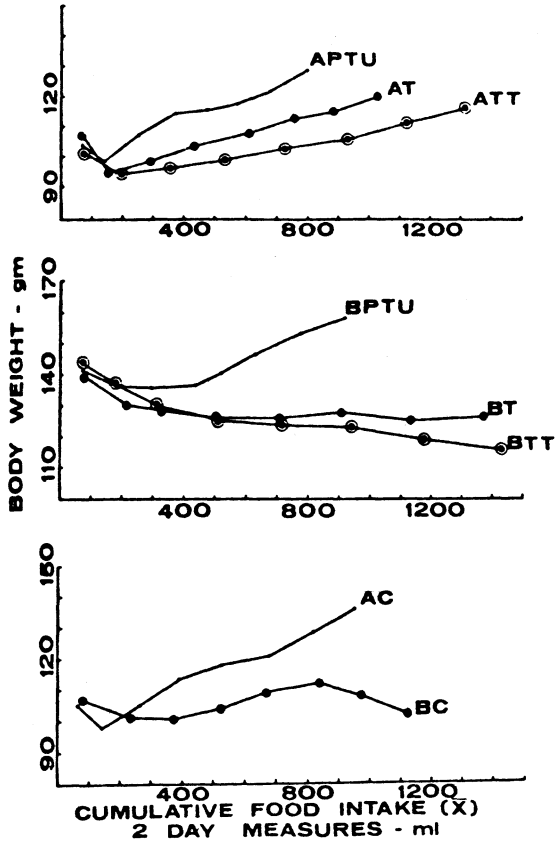

Fig. 2. Mean weight gain (grams) as a function of food intake (milliliters). Accumulated group mean food intakes are shown; therefore, groups consuming more food show data points more to the right of the graph. Similarly, groups showing more average weight gain per S show data points more to the top of the graph.

despite overconsumption of the liquid food. As in unlesioned animals, however, Group BPTU Ss ate less food than non-PTU-treated animals, but gained weight. Group BPTU animals also seemed lethargic.

Animals on solid food receiving lesions began to develop the classic hyperphagia and attendant weight gain almost immediately. Operated Ss on solid food gained significantly more weight than unoperated ($t = 5.54$, $p < .01$).

DISCUSSION

The present experiment demonstrated two main points. First, the importance of the type of food offered to lesioned Ss with regard to the development of hypothalamic obesity is apparent. Liquid diets, of the milk-type used here, did not allow the development of obesity despite the avid rate of consumption by operated animals. In all cases, except PTU-treated Ss, operated animals on liquid food consumed more food than similarly treated controls, but lost weight markedly. This points out the second combinative factor in hypothalamic obesity. The lesioned animal must have a markedly elevated metabolic rate as shown by the

weight loss, despite the increased food consumption. In support of this point, Mayer and Greenberg (1953) observed higher body temperatures in hypothalamic hyperphagic rats which were not associated with overeating and appeared prior to marked weight increases. In the present experiment, only by decreasing the metabolic rate in operated Ss—by the administration of PTU—could normal growth be produced and death and starvation be avoided. The milk diet used was sufficient to produce growth and a normal histological picture of the adrenal and thyroid glands in unoperated Ss. Even unoperated animals treated with exogenous thyroxine to increase metabolic rate gained weight on the liquid diets. It seems appropriate then to postulate a cooperative effect in the dynamic phase of hyperphagia when the animal is overeating and "overmetabolizing." The increased metabolism, however, seems to accelerate the transformation of carbohydrates to depot fats (Brobeck, 1946), rather than allow normal growth and activity.

Several explanations could be advanced to account for the above observations. Overeating could produce a subsequent rise in metabolic rate which is unaccompanied by appropriate thyroid function in operated animals. Lack of thyroid response adequate to sufficiently utilize food intakes could stem from the basomedial hypothalamic lesion interfering with the normal thyroid TSH-RF feedback mechanism or brain thyroxine reception. For example, hypotheses concerning the involvement of thyroxine in a permissive facilitation of insulin action in the physiological condition is provided by Tepperman (1968). Tepperman states that the absence of thyroid hormones and corticoids renders the primary metabolic hormones—insulin and adrenalin—metabolically less active. Thus, in the physiological condition, abnormal thyroid or adrenal function might impair the basic metabolic process, including the deposition and breakdown of fats, and may play a role in the VMH syndrome. Also, Butterfield and Whichelow (1964), as well as Tepperman, point out that thyroid imbalance—high or low levels—can cause a diabetes-like effect. The basomedial hypothalamic lesion might result in animals which are prone to the development of diabetes and metabolic anomalies which will contribute to the development of the obesity syndrome.

In the present experiment, Groups BPTU and BC point to the impairment of brain-thyroid interaction. Group BPTU did not show activation of the thyroid gland as did Group APTU Ss (both, however, showed systemic hypothyroidism), indicating an inability of the operated, PTU-treated Ss to respond to lowered systemic thyroxine levels. Group BC Ss showed marked weight loss despite overeating and no adrenal-thyroid reciprocity, indicating again the disruptive effects of the lesion on normal hormonal interactions. Adding thyroxine to operated animals only further intensified the inanition, but restored adrenal-thyroid reciprocity.

In summary, this experiment has confirmed previous reports indicating the dependence of the development of hypothalamic obesity upon the type of food offered. Also, thyroxine treatment was shown to stimulate adrenal enlargement, food intake, and depress weight gain in both dosages in control and operated Ss. PTU administration caused the opposite effects and protected the lesioned Ss from inanition under the liquid diet. Lesioned Ss consumed more food than did similarly treated controls but, with the exception of PTU-treated Ss, lost weight. The study demonstrates that metabolic disturbances (disruption of hypothalamic/thyroid interaction and thyroid-adrenal balance) underlie the phenomenon of hypothalamic obesity and suggests that the increased eating and weight gain may result from this metabolic disruption, as indicated through previously cited results of Mayer and Greenberg (1953).

REFERENCES

Brobeck, J. R. Mechanisms of the development of obesity in animals with hypothalamic lesions. Physiological Review, 1946, 26, 541-559.

Brobeck, J. R., Tepperman, J., & Long, C. H. Experimental hypothalamic hyperphagia in the albino rat. Yale Journal of Biological Medicine, 1943, 15, 831-853.

Butterfield, W. J., & Whichelow, M. J. Are thyroid hormones diabetogenic? A study of peripheral glucose metabolism during glucose infusions in normal subjects and hyperthyroid patients before and after treatment. Metabolism, 1964, 13, 620.

Hetherington, B. W., & Ranson, L. W. Hypothalamic lesions and adiposity in the rat. Anatomical Records, 1940, 78, 149.

Mayer, J., & Greenberg, R. M. Hyperthermia in hypothalamic hyperphagia. American Journal of Physiology, 1953, 173, 523-525.

Miller, N. E. Some psychophysiological studies of motivation and of behavioral effects of illness. Bulletin of the British Psychological Society, 1964, 17, 55.

Reichlin, S. Control of thyrotropic hormone secretion. In L. Martini and W. F. Ganong (Eds.), *Neuroendocrinology*. Vol. 1. New York: Academic Press, 1966.

Schmid, R., & Gonzalo, L. Über die hypothalamische Steuerung der ACTH-ablage sus der Hypophyse bei Diptheris-toxin Vergiftung. Endokrinologie, 1957, 34, 65.

Tepperman, J. *Metabolic and endocrine physiology*. Chicago: Yearbook Medical Publishers, 1968.

(Received for publication April 5, 1973;
revision received August 3, 1973.)