Maintenance of Obesity Following Hypophysectomy
in the Obese-Hyperglycemic Mouse (ob/ob)

THOMAS A. PLOCHER AND TERRY L. POWLEY
Yale University, New Haven, Connecticut
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In order to examine the role of the pituitary in the obese-hyperglycemic syndrome, obese (ob/ob) and
nonobese sibling (OB/?) mice were sham-operated or hypophysectomized by a parapharyngeal method at 60
to 90 days of age and subsequently weighed for nine weeks. Completeness of hypophysectomy was assessed by
microscopic examination of stained serial sections of the brain and attached hypophyseal capsule. Complete
hypophysectomy resulted in a moderate weight loss in the obese mice and attenuated further increases in
adiposity, but it failed to eliminate the adiposity already established prior to surgery as determined from Lee
index values. We tentatively conclude that neither the pituitary nor the target organs it controls represent the
site of the primary genetic abnormality that maintains the obesity of the ob/ob.

The obese-hyperglycemic syndrome (ob/ob) in mice, inherited as a single recessive
factor, arose in Jackson Laboratory stock in 1950. The syndrome is characterized by
excessive weight gain detectable by ten days of age [1] and by massive obesity
manifested both as hypertrophy and as hyperplasia of adipocytes [2]. In addition, the
ob/ob shows increased food efficiency [1], hyperphagia [3], infertility [3], and
hyperinsulinemia identifiable by four weeks of age, followed by hyperglycemia [4].
Recent work has indicated that the obesity of the ob/ob is "metabolic": it persists
even when the food intake of the mouse is limited to control amounts [5]. Numerous
studies, in fact, suggest that the abnormal weight gain and metabolic aberrations of
the ob/ob may well be related to a defect in endocrine function.

First, both adrenal [6] and serum [7,8] corticosterone levels are elevated in the
ob/ob. Paradoxically, although both pituitary ACTH content and basal release of
ACTH in vitro are greatly elevated in obese mice, resting plasma ACTH levels are
normal [6]. Together these observations suggest the possibility of an abnormal
episodic release of ACTH combined with normal basal secretion in the ob/ob.
Adrenalectomy reduces but does not eliminate the weight gain in the ob/ob, and it
has a therapeutic effect on the abnormal levels of blood glucose and insulin [9,10].

Second, after finding evidence for increased incorporation of sulfate into costal
cartilage in obese mice compared to normals, Herbai, Westman, and Hellerstrom
[11] proposed a possible role for increased growth hormone secretion in the syn-
drome. This suggestion is apparently at odds with recent reports of normal or slightly
depressed basal plasma levels of immunoreactive growth hormone in obese mice
[12,13], as well as with the observation that abnormal weight gain attributed to the ob
gene occurs in dwarf ob/ob mice [14]. Nonetheless, given the pulsatile nature of
growth hormone secretion [15], the possibility remains that an exaggerated phasic
release of the hormone may contribute to the syndrome.

A substantial weight loss in the ob/ob mouse following hypophysectomy was
reported by Herbai [16]. However, the lack of adequate tests for completeness, the

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admitted possibility of brain damage owing to the transauricular surgical approach, the failure to provide an optimal postoperative diet, and the rather brief observation period all make the results difficult to interpret. The object of the present study was to examine the importance of a hypothalamo-hypophyseal pathway in the expression of the obese-hyperglycemic syndrome by reassessing the effect of hypophysectomy on weight gain and adiposity. The results indicate that hypophysectomy does not eliminate the obesity established prior to surgery, but that it does attenuate its further development.

METHODS

Animals

Obese (ob/ob) mice and nonobese siblings (OB/?) were bred from matings of C57B1/6J OB/ob males and females obtained from the Roscoe B. Jackson Memorial Laboratory, Bar Harbor, Maine. Mice were weaned at 21 days of age, housed in groups, and maintained ad libitum on D and G Type 81M pellets (8% fat) (Price-Wilhoite Co.). The mouse colony was maintained at a temperature of approximately 26°C under conditions of 14 hrs of light and 10 hrs of dark. The mice were weighed three times weekly, and as a measure of linear growth, nasal-anal lengths were measured at surgery and again at sacrifice. Nasal-anal lengths were determined with the anesthetized animals lying in the supine position.

Hypophysectomy

Obese (ob/ob) mice and nonobese siblings (OB/?) of both sexes were randomly assigned to hypophysectomy (hypox) or sham-operated (sham) groups at either 60 or 90 days of age (in the final analysis each experimental group was composed of three animals that were 60 days of age at surgery and two that were 90 days of age). At surgery, the mice received an i. p. injection of .08 cc atropine sulfate (.007 g/ml) after which they were anesthetized with an i. p. injection of .025 g Tribromoethanol/cc isotonic saline (dose .015 cc/gbw). Hypophysectomy was performed according to a parapharyngeal method described by Plocher and Powley [17]. As a postoperative prophylaxis against infection, all mice received daily i. p. injections of 10% Sulfadimethoxine (Bactrovet: Pitmann-Moore Co.) in an initial dose of .0043 cc/gbw and subsequent doses of .0023 cc/gbw for one week after surgery. Dexamethasone sodium phosphate (Decadron: Merck, Sharp, & Dohme) was diluted to a concentration of .20 mg/cc isotonic saline and administered s.c. to hypophysectomized mice. Hypophysectomized nonobese siblings received an initial dose of .04 cc which decreased daily to .01 cc on the seventh postoperative day, at which time replacement therapy was terminated. In view of the reported adrenocortical hyperactivity in the ob/ob, hypophysectomized obese mice received an initial dose of .10 cc of the Decadron solution, which was decreased daily to a final dose of .01 cc ten days after surgery, when the treatment was terminated. One-half of the sham-operated obese mice and nonobese siblings were randomly designated to receive the same treatment. The mice were housed one or two per cage and, in addition to the normal pelleted diet, were given access to a wet mash composed of 84 g powdered Purina Rat Chow, 64 g Magnolia sweetened condensed milk, and 16 g sucrose in 150 ml water. The hypophysectomy mortality rate was 62% for obese mice and 37% for nonobese siblings.

Histology

Sixty days following surgery, the mice were sacrificed with an overdose of sodium pentobarbitol and perfused intracardially with normal saline followed by 10% buf-
ferred formalin. Adrenals and gonads of hypophysectomized mice were observed for signs of atrophy and, along with the livers and pancreases, were removed and stored in formalin. The heads were stored in formalin for at least one week after which the brains, with the investing membranes and hypophyseal capsule attached, were dissected from the skull under a dissecting microscope and embedded in paraffin. Serial coronal sections were cut at 5 microns and stained with cresyl violet. The sections were observed under a light microscope with a projection attachment, and the volume of any viable pituitary remnants was estimated from tracings drawn on graph paper at a magnification of 45X. The estimated volume of pituitary tissue from four sham-operated mice was used as a standard in the estimations.

Shih, Huang, and Peng [18] have demonstrated that hypophysectomized rats with pituitary remnants of less than 1% normal volume are physiologically completely hypophysectomized. This criterion of 1% was used in the present experiment. After the initial screening in which nine of the surviving mice were discarded from the experiment owing to a lack of gonadal atrophy, microscopic analysis revealed that no animal had pituitary remnants greater than 1% of normal volume. Thus, all 20 hypophysectomized mice retained for data analysis either had no pituitary remnants or remnants estimated to be less than 1% normal volume. Further microscopic examination of these 20 brains also indicated that there was no apparent damage to the median eminence or ventral brain stem due to the hypophysectomy procedure.

Data Analysis

The Lee index [19], defined as 1000 X (body weight in g) 1/3/ nasal-ocular length in cm, has been shown to be a good estimate of carcass fat content in both rats [20] and mice.1 Thus, as a measure of obesity the Lee index was computed for each of the 40 animals at surgery and again at sacrifice. All data were analyzed by analysis of variance with multiple comparisons, according to the Neuman-Keuls procedure [21].

RESULTS

Fig. 1 depicts the body-weight changes of male ob/ob mice and nonobese (OB/?) sibling males following hypophysectomy or sham-operation. Table 1 gives absolute and percentage changes in body weight from surgery to sacrifice for both male and female ob/ob and nonobese sibling mice. As illustrated in Fig. 1, male obese mice weighed significantly more than nonobese sibling males at surgery (P's < .01 by Neuman-Keuls tests). During the first week after surgery, males in all groups showed a weight loss after which both of the sham-operated groups resumed weight gain. Hypophysectomized sibling males lost weight for the first two weeks following surgery, after which their weight stabilized and remained virtually constant until sacrifice at Week 9. Male obese mice likewise responded to hypophysectomy with an initial moderate weight loss followed by stabilization of body weight at a lowered level. Multiple comparisons following a gene × hypox × sex analysis of variance on the weight change data presented in Table 1 indicated that ob/ob and nonobese sibling males did not differ significantly from each other in either their percentage weight loss or absolute weight loss response to hypophysectomy. In contrast, while both male sham groups gained weight over the nine weeks following surgery, sham-operated ob/ob males significantly outgained sham siblings in total (P < .01), but not in percentage, weight gain.

Although hypophysectomy produced a moderate weight loss in ob/ob males, Fig. 1 clearly shows that hypox ob/ob males weighed significantly more than hypox

1 Significant positive correlations between percent fat content and Lee index (r[45] = .86, p < .01) and between total carcass fat content and Lee index (r[45] = .87, p < .01) in mice have been reported by Plocher and Powley [17].
FIG. 1. Weekly body-weight values (means ± SEM) for hypophysectomized (hypox) and sham-operated (sham) obese (ob/ob) and nonobese sibling (OB/?/) males. Only the positive or negative value of SEM is given. For each group of five animals, surgery was performed at either 60 (N = 3) or 90 (N = 2) days of age.

TABLE 1
Mean (± SEM) Absolute and Percentage Change in Body Weight from Surgery to Sacrifice

| Group        | N  | % Change | Absolute Change (g) |
|--------------|----|----------|---------------------|
| ob/ob        |    |          |                     |
| ob/ob ♂ Hypox| 5  | -23.6 ± 4.0| -8.8 ± 1.5          |
| ob/ob ♂ Sham | 5  | 24.6 ± 2.3 | 15.3 ± 1.0          |
| OB/? ♂ Hypox | 5  | -26.0 ± 5.9| -6.5 ± 1.6          |
| OB/? ♂ Sham  | 5  | 18.8 ± 3.1 | 6.6 ± 1.3           |
| ob/ob ♀ Hypox| 5  | -17.6 ± 4.0| -6.8 ± 1.6          |
| ob/ob ♀ Sham | 5  | 21.6 ± 3.6 | 12.3 ± 2.0          |
| OB/? ♀ Hypox | 5  | -2.4 ± 4.5 | -0.5 ± 1.1          |
| OB/? ♀ Sham  | 5  | 21.3 ± 1.7 | 6.5 ± 0.8           |

siblings throughout the experiment (all Ps < .01 by Neuman-Keuls comparisons). Examination of the Lee indices presented in Table 2 further underscores the fact that despite the moderate weight loss following hypophysectomy, ob/ob males remained obese. The Lee index is also useful in assessing the observation that hypox ob/ob males and sham-operated nonobese siblings did not differ significantly in body weight at sacrifice. Although these two groups had similar body weights at sacrifice, Neuman-Keuls comparisons showed that hypox ob/ob males were both significantly shorter than sham sibling males (8.49 cm vs. 9.37 cm, P < .01) and more obese (389.6 vs. 342.7, P < .01).

Fig. 2 is a photograph of typical animals from each of the four male groups at sacrifice. It is obvious from Fig. 2 that the hypox ob/ob is still massively obese
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TABLE 2
Mean (± SEM) Nasal-anal Length and Lee index at Surgery and at Sacrifice

| Group      | N | Nasal-anal length (cm) | Lee index* |
|------------|---|------------------------|------------|
|            |   | Surgery     | Sacrifice  | Surgery     | Sacrifice  |
| ob/ob 🅀  | 5 | 9.23 ± .08  | 8.49 ± .10 | 386.9 ± 3.9 | 389.6 ± 1.4 |
| ob/ob 🅀  | 5 | 9.16 ± .20  | 9.65 ± .17 | 392.1 ± 2.9 | 405.9 ± 6.3 |
| OB/♀ 🅀   | 5 | 9.16 ± .12  | 8.69 ± .19 | 342.0 ± 3.5 | 330.7 ± 6.7 |
| OB/♀ 🅀   | 5 | 9.93 ± .07  | 9.37 ± .11 | 337.5 ± 3.7 | 342.7 ± 4.5 |
| ob/ob 🅀  | 5 | 9.11 ± .12  | 8.40 ± .18 | 388.9 ± 5.3 | 396.7 ± 5.2 |
| ob/ob 🅀  | 5 | 9.11 ± .09  | 9.43 ± .12 | 386.6 ± 5.1 | 402.4 ± 4.2 |
| OB/♀ 🅀   | 5 | 8.55 ± .08  | 8.19 ± .10 | 333.0 ± 3.3 | 344.7 ± 3.2 |
| OB/♀ 🅀   | 5 | 8.57 ± .11  | 9.07 ± .11 | 333.1 ± 3.0 | 340.5 ± 4.8 |

*Lee index = (√body weight / nasal-anal length) × 1000

FIG. 2. Photograph of one animal from each of the four male groups 60 days after hypophysectomy or sham-operation.
Group abbreviations are: OBESE = obese-hyperglycemic (ob/ob) mouse; SIBLING = nonobese (OB/?) sibling; HYPOX = hypophysectomized; SHAM = sham-operated.

compared to either the hypox or the sham-operated nonobese sibling. The figure also shows the shorter nasal-anal lengths of the hypox animals compared to the sham animals.

Fig. 3 shows the body weight changes of female ob/ob and nonobese sibling mice during the nine weeks following hypophysectomy or sham-operation. It can be seen from Fig. 3 that ob/ob females responded to hypophysectomy in a manner similar to ob/ob males. Hypox ob/ob and sibling females both showed a moderate weight loss after surgery. After Week 1, hypox ob/ob females became nearly stabilized at the lower body weight level with only a slight loss of weight during the next eight weeks. Following an initial postoperative weight loss, hypox sibling females gradually gained weight and, by Week 9, had nearly attained their preoperative weight. Although weight gain was obviously retarded in the two hypox groups, multiple comparisons following gene × hypox × sex analysis of variance showed that both the
percentage and net weight losses of ob/ob females following hypophysectomy were significantly greater than those of hypox sibling females (P's < .01). In addition, sham-operated ob/ob females showed a significantly greater total (P < .01), but not percentage, weight gain during the nine weeks than sham sibling females.

Although ob/ob females lost more weight than sibling females following hypophysectomy, they significantly outweighed both sham and hypox sibling females throughout the experiment (P's < .01) and, like hypox ob/ob males, maintained a substantial obesity. Multiple comparisons following a gene × hypox × sex analysis of variance on Lee index values at sacrifice clearly showed that hypox ob/ob females were significantly more obese than their nonobese sham and hypox counterparts (P's < .01).

It is apparent from the above observations that hypox ob/ob mice are capable of maintaining a substantial obesity. The very slight increases from surgery to sacrifice in Lee index values of hypox obese mice compared to sham ob/ob controls, together with the moderate weight loss following hypophysectomy in the obese mice, suggest that hypophysectomy might have attenuated further development of the obesity. Comparison of initial and final Lee indices by a gene × hypox × sex repeated-measures analysis of variance indicated that, although final Lee indices of hypophysectomized obese mice tended to be slightly greater than those at surgery, the increase from surgery to sacrifice was nonsignificant. In contrast, a similar comparison showed that final Lee indices of sham-operated ob/ob mice were significantly increased over starting values (P < .01).

Finally, and as reported before [17], no effect of the Decadron treatment on the body weights of the sham-operated mice was detected.
DISCUSSION

The results of the present experiment demonstrate that, when inadvertant brain damage due to surgical approach is avoided and when adequate postoperative care is provided, complete hypophysectomy does not eliminate the obesity of the ob/ob mouse. Our hypophysectomized obese mice maintained a massive state of overweight compared to hypophysectomized siblings, and did not show a significant decrease in adiposity as measured by the Lee index. On the other hand, hypophysectomy apparently does attenuate the continued development of obesity in the ob/ob mouse.

Despite their maintenance of a substantial obesity, hypophysectomized obese mice showed a moderate postoperative weight loss. This weight loss appears not to be the consequence of illness or general debility but rather to represent the same type (and proportional degree) of reduction in body weight and composition typically reported for nonobese animals following hypophysectomy. First, the bulk of the weight loss occurred during the first few weeks following surgery, after which weight stabilized and decreased only slightly over the remainder of the experiment. Furthermore, another genetic obesity, that of the Yellow (Ay/a) mouse, on the same strain background, develops quite unhindered by hypophysectomy under identical maintenance conditions [17]. Alternatively, a comparison of the posthypophysectomy weight loss of ob/ob mice with that of their nonobese sibling controls suggests that ob/ob mice, in contrast to Yellow obese mice, display a fairly normal body weight response to hypophysectomy. Normal rats respond to hypophysectomy by wasting both fat and protein so that, despite a weight loss, the proportions of carcass constituents remain fairly constant [22]. Similarly hypophysectomized nonobese C57B1/6J mice also retain a nearly normal carcass composition in the presence of a moderate weight loss [17]. Thus, it is reasonable that—as the Lee indices suggest—the moderate weight loss displayed by hypophysectomized ob/ob mice in the present experiment was accompanied by little or no decrease in adiposity.

A significant decrease in nasal-anal length was also observed in hypophysectomized obese and sibling mice. Hypophysectomy typically produces severe atrophy of genital tissues and a loss of muscle tone possibly due to the abnormal utilization of body protein mentioned above [22]. Both factors would tend to shrink perineal tissue and produce a decrease in nasal-anal length. It should be added that all operated mice in the present experiment which did not show a decrease in nasal-anal length at sacrifice were subsequently found to have incomplete hypophysectomies. Similar results for nasal-anal length have also been obtained in other hypophysectomy experiments using the same measurement procedure [17,23].

Given the present data, several conclusions can be made about the role of hypothalamo-hypophyseal pathways in the etiology of this obesity syndrome. If the obesity of the ob/ob were actively maintained by a primary hypersecretion of the pituitary or its target organ hormones, hypophysectomy of two or three month old obese mice should have not only attenuated further development of the obesity, but also eliminated any obesity established prior to surgery. Although hypophysectomy may retard the rate of lipolysis [24], hypophysectomized animals do lose fat [17,22], and the long survival times used in the present experiment should have ensured that any lipolysis—even retarded lipolysis—encouraged by removing the active source of the obesity would have occurred. However, since the hypophysectomized mice in this experiment remained obese despite an initial moderate weight loss, hypersecretion of the pituitary or its target organs cannot be the sole primary defect underlying the syndrome. It is, of course, plausible that the ob/ob's excess number of fat cells
produced by hyperplasia [2] is responsible for sustaining much of the previously established obesity in the absence of the pituitary.

While hypophysectomy did not eliminate the obesity already established by ob/ob mice at the time of surgery, it did attenuate further development of obesity. This result suggests that pituitary or pituitary-controlled secretions might have a permissive role in supporting obesity development. Two possible mechanisms by which the pituitary might act permissively to make possible the continued development of obesity in the ob/ob mouse are particularly worthy of consideration. First, it is well known that the pituitary is necessary for the normal long-term function of the pancreatic islets [25,26,27]. A depression of both the rapid initial phase and the slowly rising second phase of insulin secretion to a glucose stimulus has been reported in isolated perfused pancreases of hypophysectomized rats [25]. Glucose-stimulated insulin biosynthesis is also depressed following hypophysectomy [26]. Furthermore, replacement therapy in hypophysectomized rats with either ACTH or hydrocortisone restores both phases of the secretory response to glucose [25] while growth hormone therapy restores the second phase of insulin secretion [25] and corrects the depressed glucose-stimulated insulin biosyntheses [27]. As Genuth, Przybyski, and Rosenberg [4] have suggested, the primary abnormality in the obese mouse might be an exaggerated insulin secretory response to the prevailing level of glucose stimulation, perhaps potentiated by an elevated release of a gastrointestinal insulinogogue, resulting in hyperinsulinemia and obesity. If the work on islet function in hypophysectomized rats generalizes to mice with the ob/ob genotype, then hypophysectomy, by depressing the sensitivity of insulin biosynthetic and secretory mechanisms to glucose, might render less effective the potentiating effects of any abnormal neural or hormonal insulinogogue. With such an attenuation of the insulin response, weight gain might well be attenuated also. While serum insulin levels were not measured in the present study, adrenalectomy of obese mice reportedly produces a substantial reduction in serum insulin levels, along with a reduction in weight gain [9].

A second mechanism by which the pituitary may act permissively in the ob/ob syndrome is suggested by the observation that hypophysectomy in the rat nearly abolishes the formation of primordial fat cells [28]. If the work on rats also generalizes to mice, then hypophysectomy in the ob/ob should prevent further hyperplasia of fat cells. Furthermore, Herberg and his co-workers [29] have shown that fat cell size in the ob/ob reaches a maximum at two–three months of age. As suggested by these authors, the continued abnormal fattening and weight gain of the ob/ob after this time can only be understood in terms of a continued hyperplasia of fat cells. If continued increases in adiposity after two to three months of age rely mainly on fat cell hyperplasia, and if hypophysectomy indeed blocks adipocyte hyperplasia in the ob/ob, then the attenuation of further increases in adiposity along with the maintenance of previously established obesity seen in the present experiment can be understood. Hypophysectomy of the genetically obese Zucker rat (fa/fa) also results in an attenuation of further increases in adiposity without eliminating the obesity present at surgery [23]. It is noteworthy that the ob/ob mouse and Zucker rat are the only rodent obesities that rely predominantly on adipocyte hyperplasia as a means for excessive fat accumulation [2,30]. It is tempting to speculate that the pituitary plays a similar, permissive role in the abnormal fat cell hyperplasia of both the ob/ob mouse and Zucker rat. Furthermore, the similarities between the two models of obesity suggest that a classification of obesities according to adipocyte cellularity may well be heuristically valuable in understanding the various etiologies of obesity. Studies of adipocyte cellularity in hypophysectomized ob/ob mice and Zucker rats at several stages of development are obviously needed to evaluate these hypotheses.
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Thomas A. Plocher
Terry L. Powley
Department of Psychology
Yale University
New Haven, Connecticut 06520