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Research Article

Modeling leptin receptor insensitivity by comparing how leptin or leptin receptor mutations in mice affect body weight, basal metabolism, body temperature and feeding behaviors

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Abstract. Leptin, a protein hormone produced principally in adipose tissue, plays a major role in the regulation of food intake, hunger, satiety and metabolism. Most obesity is likely the result of the body's resistance to leptin. The purpose of this experiment was to model leptin receptor insensitivity by comparing how the lack of leptin or the leptin receptor in mutant mice would affect body weight, basal metabolism, body temperature and feeding behaviors. Eighteen mice were used: 6 controls, 6 mutant *ob/ob* (defective for the expression of leptin), and 6 mutant *db/db* (defective for the expression of the leptin receptor). After 24 weeks of free access to food and water, the *ob/ob* mice weighed more than the control and *db/db* mice (P=0.0012). Both the *ob/ob* and *db/db* mice had lower metabolic rates (P = 0.0194) and body temperatures (P < 0.0001). As expected, the *db/db* mice had the greatest water intake (P=0.0060) and cage waste (P=0.0499) reflective of their diabetic state. The normal mice ate more than the other mice, but the increases were not significant; the *ob/ob* mice had much less food debris. These results indicate that mutations in the leptin protein or receptor interrupt normal metabolism in a manner similar to what may be experienced by individuals resistant to leptin. If a chronic intake of excessive calories results in increased adipose depositions, then over a lifetime, cell signaling activities may act to protect the leptin receptor from over bombardment by leptin, attenuate leptin's regulatory function, and promote obesity.

Introduction

Obesity is one of our nation's most pressing health problems. Many individuals struggle with the condition of being overweight, whether it is slight or excessive. Body Mass Index (BMI) is a measure of the appropriateness of a person's weight for their height, and is often used as an indicator of a healthy body weight (CDC, 2009). Adults who fall into the healthy body weight category (BMI 18.5-24.9) are in energy balance; their calorie intake generally equals their energy output. For adults who fall in the overweight (BMI 25.0-29.9) or obese category (BMI > 30), their caloric intake is in excess of their energy output, and the extra energy is not wasted but is stored compactly as fat.

Statistics show that 66% of adults ages 20 and older are overweight; 32.1% are obese. In addition, 17-17.5% of children ages 6-19 were

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overweight in the years 2001-2004 (NCHS, 2006). While it is encouraging that the increased rate in adult obesity may be leveling off (CDC, 2007), it is still taking a health toll on Americans. The statistics ten years ago were already alarming: being overweight and physically inactive accounted for more than 300,000 premature deaths in the U.S. on an annual basis, second only to tobacco-related deaths (Hensley, 1999). Medical expenses associated with overweightedness and obesity accounted for 9.1% of total U.S. medical expenditures in 1998 (Finkelstein et al., 2003).

Many individuals experience frustration in not knowing or understanding the reasons for their obesity. It is discouraging when well-intended efforts are put forth in an attempt to assist or 'fix' the weight problem, but don't yield fruitful results. Despite this, most remain motivated with the encouragement that even a modest 5% decrease in total weight loss greatly reduces their health risks (Blackburn, 1995).

There is extensive debate over the causes of overweightedness and obesity. Current theories propose that environmental factors (e.g. family eating habits, improper nutrition, lack of exercise), diseases and drugs, heredity related issues, and genetic mutations resulting in an improper balance of hormones may all contribute to weight management problems.

A particular hormone of interest in understanding obesity is leptin, a protein hormone produced principally in adipose tissue (Zhang et al., 1994). Plasma levels of leptin correlate with adipose tissue and drop with weight loss (Maffei et al., 1995). When leptin circulates in the blood and reaches the hypothalamus, it binds to leptin receptors (Williams et al., 2009) and helps inhibit food intake by reducing or controlling appetite, and increases energy expenditure and metabolism (Friedman, 2002). Normally, an increase in fat deposition should signal a decrease in appetite until fat stores are utilized. Then leptin levels should drop and the suppression of satiety be withdrawn. This feedback cycle repeats itself as eating resumes and adipocyte activity increases (Friedman and Halaas, 1998). Malfunction of the leptin protein-receptor signal would definitely interfere with normal appetite, metabolism, and weight management.

Most obese individuals sustain high levels of circulating leptin (Considine et al., 1996) and have normal expression of the leptin receptor (Farooqi and O'Rahilly, 2008). This may infer that the leptin receptor is resistant to the leptin protein, and, as a consequence, the feedback signals controlling appetite and weight gain are inhibited. Do increased plasma levels of leptin associated with weight gain lead to a down-regulation of leptin receptors (Friedman and Halaas, 1998)? If a signal molecule such as leptin is present in abnormally high concentrations in the body, target cells may attempt to decrease the number of signal receptors in order to bring a response back to normal (Silverthorn, 2010). It may be that high plasma levels of leptin, as seen in obese individuals, may actually decrease the expected leptin protein-leptin receptor signal and challenge the homeostasis of appetite, energy expenditure, and weight control.

Personal communications with obese individuals who have seriously attempted weight loss report that they do not eat more food than trim people. Instead, they lack energy, they sense their metabolism is low, and they frequently feel chilled. If leptin receptors from obese individuals are indeed resistant to the endogenous production of leptin, then the physiological changes in weight gain, metabolism, body temperature, and feeding behaviors should be comparable to organisms that have either no expression of the leptin hormone, or no expression of the leptin receptor.

The purpose of our experiment herein was to determine if the lack of expression of either the leptin hormone or the leptin receptor in mutant mice would affect body weight, metabolism, body temperature, and feeding behaviors. Results may then be compared to similar physiological changes as observed in obese people, potentially demonstrating that they may exhibit leptin receptor insensitivity.

Materials and Methods

Specimens

Eighteen mice were used in this experiment: 6 controls, 6 mutant *ob/ob*, and 6 mutant *db/db*.

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All were females and purchased from Harlan (Indianapolis, IN). The control group mice [Hsd:ICR (CD-1)] were normal white lab mice. The obese *ob/ob* group was mutant mice [B6.V-Lep^{ob}/OlaHsd] with a defective leptin gene coming from *Lep^{ob}*, an autosomal recessive mutation on chromosome 6. This leaves the mice leptin protein deficient and they exhibit obesity at 4-5 weeks of age (Harlan, 2007). The obese *db/db* group were mutant mice [BKS.Cg -+ Lepr^{db}/+ Lepr^{db}/OlaHsd] with a defective leptin receptor gene coming from *Lep^{db}*, an autosomal recessive mutation on chromosome 4. This leaves the mice leptin receptor deficient and they exhibit obesity around 3-4 weeks of age (Harlan, 2007). Mutations in the *db/db* mice result in an obese phenotype identical to the *ob/ob* mutants (Li et al., 1998).

The mice were housed in the animal facility in the Department of Biological Sciences at Bethel University, maintained on a 12-hour light dark cycle, and had access to food and water *ad libitum*. This project took place during the spring and summer of 2007, lasted for 24 weeks, and was in compliance with the university's standards and guidelines for animal care.

Experimental Design

The variables tested using the mouse groups were changes in body weight, basal metabolic rate, body temperature, feeding behaviors (such as food intake, water intake and cage waste production), and blood glucose levels.

Body weight. Body weight (g) was recorded for the initial spring and later fall metabolic rate measurements. ANOVA was used to determine if body weights among the three treatment groups {control, *ob/ob*, *db/db*} were different from each other in the spring and in the fall. Body weights were also analyzed within groups to determine if the weight gain over the course of the experiment changed significantly.

Basal Metabolic Rate. Metabolic rates (g-cal/hr/cm^2) were tested on all eighteen mice during the spring semester and again two months later, during the summer. The metabolic chambers were purchased from Carolina Biological (catalog # WF – 68 – 2000) and measurements were taken using the accompanying instructions (developed by Drs. T. D. Kimbrough and G. C. Llewellyn of Virginia Commonwealth University). An average of six repetitions in measurement per mouse were taken. Data were expressed as means ± standard error of the mean (S.E.M.) for each treatment.

Body temperature. Rectal body temperature (°C) was taken with a cryo-thermometer (Model BAT-5, Bailey Instruments Inc., Saddle Brook, NJ) on all eighteen mice at 1300 hrs every other day for six days. Data were expressed as means ± S.E.M. for each treatment.

Feeding behaviors. Food intake (g), water intake (g) and cage weight (g) from all nine cages (3 cages/treatment, 2 mice per cage) were recorded during week 20 for a seven-day period of time. The cage weight measurements included both the weight of the cage and the cage waste contents. Cages were all of the same size, composition, manufacture, and were regularly given equal masses of cage litter. Thus, any changes in weight would indicate an accumulation of urine, feces, food debris, and moisture from water drips. Weekly data were expressed as means ± S.E.M. for each treatment.

Blood glucose. The *db/db* mice were expected to demonstrate elevated plasma insulin levels at 10-14 days age and hyperinsulinemia at 4-8 weeks of age, despite severe depletion of pancreatic islet insulin producing B-cells (Harlan, 2007). At the end of the experiment, blood glucose levels (mg/dl) were collected from all eighteen mice to verify that the *db/db* mice were indeed diabetic and that the *ob/ob* and normal mice were not. Blood samples were collected from the tail vein. Glucose was measured using an OneTouch® Ultra glucose meter and levels were expressed as means ± S.E.M. for each treatment. Normal blood glucose in mice is considered to be 62-175 mg/dL (Harkness and Wagner, 1989).

Statistical Analyses

To test the null hypotheses that a mutation in either the genetic expression of the leptin protein or the leptin receptor had no effect on body weight, basal metabolic rate, food intake, water intake, cage waste, body temperature, and blood

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glucose levels, ANOVA was performed to determine if the three treatment groups (control, *ob/ob*, *db/db*) were different from each other. In all analyses, the Tukey-Kramer HSD served as a *post hoc* test to determine which means were statistically different from each other. Results were considered to be significant at $p \leq 0.05$ (JMP, 2001).

Results

The results indicate how the lack of leptin or the leptin receptor in mutant mice affected their body weight, basal metabolism, body temperature, feeding behaviors, and blood glucose levels.

Body weight. Figure 1 illustrates what the mice looked like after six months of free access to food and water. At the end of the experiment, the average mass (n=6) for each treatment group was: control 50.6g; *ob/ob* 69.9g; and *db/db* 54.1g. Although the observed mobility of the *ob/ob* mice was greatly reduced, they were still able to access food and water. Post mortem examinations clearly showed the greatest increase in fat pad size was seen in the *ob/ob* mice.

The mean weights (± S.E.M.) for each of the treatment groups during the spring and summer are shown in Figure 2. There was no significant difference in the weights of the treatments groups when initial measurements were taken in the spring (P=0.1438). However, the summer weights of the *ob/ob* mice at the end of the investigation were greater than both the control and *db/db* weights (P=0.0012). The summer weights of the control mice and the *db/db* mice were not different from each other.

Both the control mice and the *ob/ob* mice experienced significant increases in body weight from spring to summer (P=0.0478 and P=0.0007, respectively). The *db/db* mice did gain weight over the time course of the experiment, but the increase was not significant (P=0.0821).

Metabolic rates. The mean basal metabolic rates (± S.E.M.) for each of the treatment groups taken during the spring and summer are shown in Figure 3. The control mice in the spring had a greater metabolic rate than the *db/db* mice, and a significantly greater rate than the *ob/ob* mice (P = 0.0463). The magnitude of this difference increased even more during the summer with the control mice having a statistically greater metabolic rate than both the *ob/ob* mice and the *db/db* mice (P = 0.0194). Metabolic rates within each treatment group, however, did not vary between spring and summer (control, P = 0.4725, *ob/ob,* P = 0.3784, *db/db,* P = 0.1686).

Body temperature. Mean rectal body temperature (± S.E.M.) for each of the treatment groups of mice are shown in Figure 4. The control mice

Figure 1. A side-by-side comparison how mice from each treatment group looked after six months food and water *ad libitum*. From left to right they are control, *ob/ob* mice, and *db/db* mice; only the mutant mice had dark colored coats.

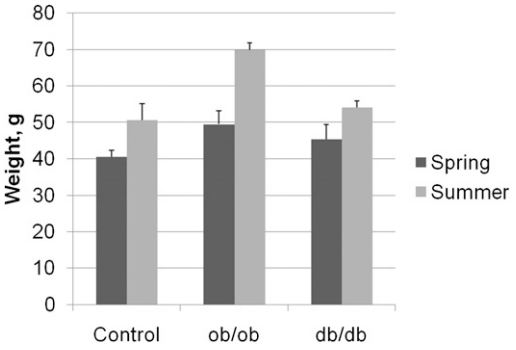

Figure 2. Mean weight (± S.E.M.) for each of the treatment groups during the spring and summer of 2007. While there was no significant difference in the initial weights among the treatments groups taken in the spring, the summer weights of the *ob/ob* mice at the end of the investigation were greater than both the control and *db/db* weights. Both the control mice and the *ob/ob* mice experienced a significant increase in body weight over the course of the experiment. Sample size was 6 for each treatment group.

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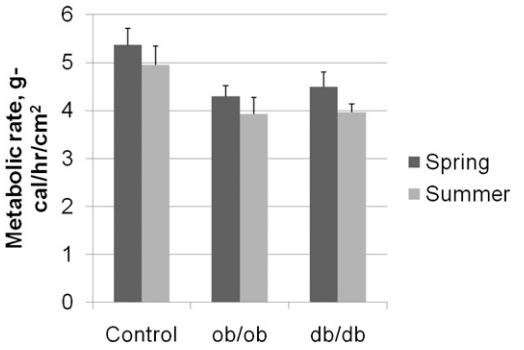

Figure 3. Mean basal metabolic rates (± S.E.M.) for each of the treatment groups during the spring and summer of 2007. By the end of the investigation, the control mice had a statistically greater metabolic rate than both the *ob/ob* mice and the *db/db* mice. Metabolic rates within each treatment group did not vary in between spring and summer measurement. Sample size was 6 for each treatment group.

had statistically higher body temperatures than both the *ob/ob* mice and the *db/db* mice ($P < 0.0001$).

Feeding behaviors. The mean food intake, water intake, and cage weight (± S.E.M.) for each of the treatment groups of mice are shown in Figure 5. While the control mice had greater food intake than the *ob/ob* and the *db/db* mice, the increase was not significant ($P = 0.1443$).

The mean water intake (± S.E.M.) for the *db/db* mice was statistically greater than both the *ob/ob* mice and the control mice (Figure 5, $P = 0.0060$). Similarly, the mean cage waste (± S.E.M.) of the *db/db* mice was greater than the control mice and statistically greater than the

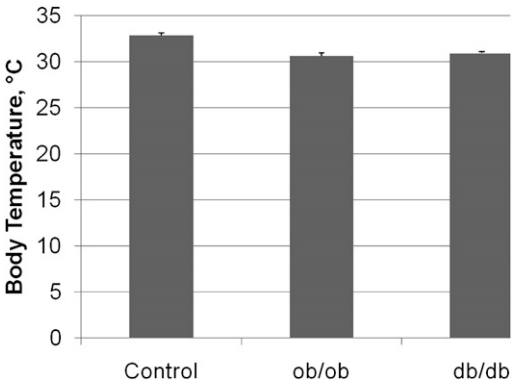

Figure 4. Mean rectal body temperature (°C) (± S.E.M.) for each of the treatment groups. The control mice had statistically higher body temperatures than both the *ob/ob* mice and the *db/db* mice. Sample size was 6 for each treatment group.

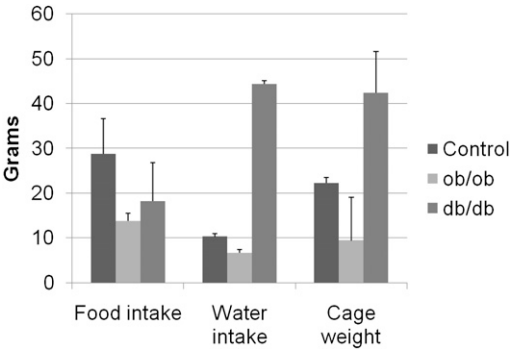

Figure 5. Mean (± S.E.M.) food intake (g), water intake (g), and cage weight (g) for each of the treatment groups of mice. The control mice had greater food intake than the *ob/ob* and the *db/db* mice. The *db/db* mice water intake and the cage weight (including waste) was greater than both the *ob/ob* mice and the control mice. Sample size was 6 for each treatment group.

ob/ob mice ($P = 0.0499$). This outcome was expected as the diabetic *db/db* mice should have increased their water consumption to replace the high volume of water excreted in the urine as glucosuria-induced osmotic diuresis (Silverthorn, 2010).

The cage weight of the control mice was greater than that of the *ob/ob* mice (Figure 5) even though the *ob/ob* mice gained more weight than the control mice (Figure 2). Upon review of the cage contents, it was observed that the feeding habits of the control mice were very messy, leaving large pieces of food debris piled all throughout the cage litter. The *ob/ob* mice were very clean and very little observable food waste was found in their containers.

Blood glucose. Mean blood glucose levels (± S.E.M.) for each of the treatment groups of mice are shown in Figure 6. As expected, *db/db* mice had statistically higher blood glucose levels (563 mg/dl) than both the *ob/ob* mice and the control mice ($P < 0.0001$). While the *ob/ob* mice had slightly elevated blood glucose levels (148 mg/dl) when compared to the controls (118 mg/dl), they were not considered to be diabetic as their blood glucose was < 200 mg/dl (Talubmook et al., 2003).

Discussion

The proper signaling of leptin to its receptor plays a major role in the regulation of food intake,

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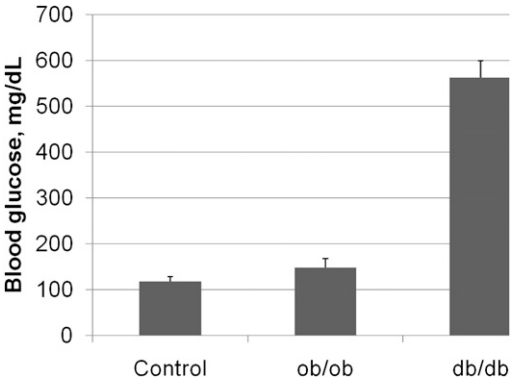

Figure 6. Mean blood glucose levels (mg/dL) (± S.E.M.) for each of the treatment groups. The *db/db* mice had statistically higher blood glucose levels than both the *ob/ob* mice and the control mice. Sample size was 6 for each treatment group.

hunger, satiety and metabolism (Badman and Flier, 2007). In this investigation we showed that mutations in the genetic expression of either the leptin protein or the leptin receptor in mice disrupts the leptin signaling mechanism and resulted in weight gain, lower metabolic rate, depressed body temperature, and altered feeding patterns, all of which may contribute to obesity. Clement et al. (1998) found that humans with a mutation in the leptin gene were associated with early-onset obesity and a reduced secretion of the thyroid hormone which is essential for proper metabolism. However, mutations in the expression of the leptin protein and the leptin receptor in humans are rare and are estimated to occur in only 1% and 2-3% of the population, respectively (Farooqi and O'Rahilly, 2008). Therefore it is important to recognize that obese individuals may be experiencing leptin receptor desensitization to their own leptin production.

Most overweight and obese individuals have a significantly higher concentration of leptin circulating in their blood than do normal weight individuals (Maffei et al., 1995; Considine et al., 1996). The more food consumed concurrent with the increase in adipose tissue, the more leptin is released. These individuals are considered to become resistant to the effects of leptin (Frederich et al., 1995), perhaps analogous to the way that people with type 2 diabetes become resistant to the effects of insulin (Friedman and Halaas, 1998).

It is a challenge for researchers to figure out exactly how leptin receptor desensitization occurs. Zabolotny et al., (2002) was able to show that a deficiency in the PTP1B signaling molecule (protein tyrosine phosphatase, non-receptor type 1) attenuated weight gain in mice, which were lacking normal hypothalamic leptin signaling. Mori et al., (2004) and Dunn et al., (2005) further demonstrated that a deficiency in Socs3, a suppressor of cytokine signaling in hypothalamic neurons, elevated leptin sensitivity and could be a potential therapy for leptin-resistance in obesity. Overconsumption of food over a lifetime that results in the consistent release and elevation of leptin may initiate signal molecules such as these to protect the cell by preventing the leptin from binding to the receptor, and as a result increase receptor resistance (Flier and Maratos-Flier, 2007).

Receptor desensitization was modeled in this experiment by using mutant mice. The *ob/ob* mutant mice did not express the leptin hormone, but did express a functional leptin receptor. The *db/db* mutant mice did not express the leptin receptor, but did express the protein. Hence both mutant mice treatment groups had impaired protein receptor communication. This may mimic the impaired human leptin signaling induced by the over production of leptin and the inferable desensitization of leptin receptors. Consequentially, the absence of leptin's inhibitory effect on the postulated hypothalamic satiety center results in overeating and obesity (Wolff, 1997). Unfortunately, it would seem that as more adipocytes are stored, more leptin would be produced in an effort to try to feedback and correct this problem.

Future studies are needed in order to determine whether or not leptin receptors can become re-sensitized. People go on diets and do experience some success in weight loss. If adipose tissue is reduced and the production and release of leptin is decreased, can it be expected that signal molecules preventing the overstimulation of leptin receptors will be suppressed? Then normal leptin-receptor signaling and appetite can be suppressed relative to fat storage. It has been shown in humans that diet-induced weight loss does reduce plasma leptin levels, but it also

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resulted in a decreased metabolic rate (presumably conservative), and increased appetite (Friedman, 2002). Animals are compelled to eat voraciously when extremely low levels of leptin are associated with low body fat due to starvation (OHSU, 1997).

The target sites for leptin in the brain trigger the production of the active form of a small protein called alpha-melanocyte-stimulating hormone (áMSH) located in the hypothalamus. This peptide is said to be one of the body's most powerful metabolism booster signals, sending a fast, strong message to the brain to burn calories and increase body temperature. áMSH signals the pituitary gland to produce and secrete thyroid-stimulating hormone thus activating thyroid hormone pathways to increase cellular energy production, which in turn elevates body temperature (Sanchez et al., 2004). áMSH also sends a signal to another target site in the hypothalamus to regulate the pathway for satiety (Badman and Flier, 2007). Therefore, if the initial áMSH pathway is not triggered by leptin protein-receptor signaling, satiety, metabolic rate, and body temperature can be affected.

Individuals who struggle with weight control often claim they have less energy, presuming this to be an indicator of a depressed metabolic rate; this was observed in our *ob/ob* mutant mice (Figure 3). Astrup et al. (1996) found an eight percent reduction in metabolic rate (for a given body composition) among postobese women with a family history of obesity (compared with a closely matched control group). The women also had depressed thyroid hormone concentrations, which statistically could explain their lower resting metabolic rate. It may be inconclusive, however, to explain energy metabolism as a possible explanation of obesity because there is a wide range in energy expenditure in the population, even after adjusting for body composition (Meyer et al., 2004).

In summary, it would seem that the increase in weight gain, lowered metabolism, depressed body temperature, and altered feeding behaviors as seen in mutant mice having no expression of the leptin protein or receptor, are comparable to the physiological changes communicated by obese individuals. This may infer that they are experiencing receptor desensitization to their own leptin. Researchers were very disappointed to find that when leptin injections were given to humans as treatments to aide in weight loss, the results were poor and inconsistent (Flier and Maratos-Flier, 2007).

Goran (2000) suggests that the major dependent variable that needs to be examined in relation to the cause of obesity may be energy balance over time. The importance of understanding and practicing food consumption in moderation over a life time is likely the most important step an individual can take to prevent the onset of leptin receptor desensitization. Leptin receptor signaling is an extremely important physiological regulator of appetite and metabolism; the application of the results herein indicate that our behaviors regarding food intake is one component that we may have some control over in future battles to prevent obesity.

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