

Outstanding Scientific Achievement Award Lecture 2010: Deconstructing Leptin: From Signals to Circuits

Martin G. Myers Jr.

Martin G. Myers Jr., MD, PhD, received the American Diabetes Association's prestigious 2010 Outstanding Scientific Achievement Award at the Association's 70th Scientific Sessions in Orlando, Florida, on 28 June 2010. The Outstanding Scientific Achievement Award recognizes outstanding scientific achievement in the field of diabetes, taking into consideration independence of thought and originality.

Currently the Marilyn H. Vincent Professor of Diabetes Research at the University of Michigan, Ann Arbor, and Associate Professor in internal medicine and in molecular and integrative physiology at the University of Michigan Medical School, Dr. Myers began his impressive track record in diabetes research as a graduate student in the laboratory of Dr. Morris White at the Joslin Diabetes Center/Harvard Medical School. There, Dr. Myers deciphered many of the insulin signaling pathways engaged by insulin receptor substrate proteins.

Following his graduation from the Harvard MD-PhD Program in 1997, Dr. Myers was promoted to instructor in medicine at the Joslin Diabetes Center/Harvard Medical School. He began his independent work by building a molecular framework for understanding the mechanisms of leptin signaling, including how individual phosphorylation sites on the leptin receptor recruit distinct signaling molecules. He was promoted to assistant professor at Harvard in 1999.

In 2004, Dr. Myers moved to the University of Michigan, where he built upon the molecular framework of leptin signaling to probe the regulation of metabolism by individual leptin signals. Dr. Myers' laboratory revealed the specificity of leptin signals in metabolic control, including the role for leptin-STAT3 signaling in the regulation of energy balance and glucose homeostasis. His group also defined roles for leptin receptor feedback inhibition and hypothalamic mTor signaling in metabolism.

Dr. Myers' laboratory has recently developed novel molecular approaches to elucidate the leptin-regulated brain circuits that contribute to metabolic control, enabling the discovery of novel brain systems and their functions.

In 1998, Dr. Myers received the American Diabetes Association's Career Development Award for his scientific abilities. Dr. Myers' current support includes the National Institute of Diabetes and Digestive and Kidney Diseases MERIT Award. *Diabetes* 59: 2708–2714, 2010

From the Department of Medicine, Division of Metabolism, Endocrinology and Diabetes, University of Michigan Medical School, Ann Arbor, Michigan. Corresponding author: Martin G. Myers Jr., mngmyers@umich.edu. DOI: 10.2337/db10-1118

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The scientific tale that I share in this article actually began decades ago, with the discovery of two independent mutant mouse strains at the Jackson Laboratory. The obese (*ob/ob*) and diabetic (*db/db*) strains suffer from an identical set of problems: they are obese, they have type 2 diabetes, and a variety of their endocrine systems are disrupted in a pattern reminiscent of the response to starvation.

Early studies, also carried out at the Jackson Laboratory, predicted that the gene affected in the *ob/ob* mouse is a hormone, while the receptor for that hormone is disrupted in *db/db* mice. Indeed, when the *ob* gene was cloned by the laboratory of Jeff Friedman 15 years ago, it was found to encode a hormone, which was named “leptin.”

Leptin is produced by fat cells. To a reasonable approximation, the more energy (fat) is stored in a fat cell, the more leptin the cell produces and secretes into the circulation. Circulating leptin makes its way to the brain, where it binds to the leptin receptor. Subsequent to the identification of leptin, the cloning of the leptin receptor revealed that this gene was disrupted in *db/db* mice.

Different parts of the brain mediate distinct functions, and only a few parts of the brain express the leptin receptor. As one might expect, the leptin receptor is expressed at particularly high levels in the hypothalamus, which is the region of the brain that controls a great deal of food intake, glucose homeostasis, and endocrine function. Leptin action via leptin receptors in the brain suppresses appetite and hepatic glucose production (thereby modulating the amount of glucose in the blood). Leptin also signals that the long-term energy stores in fat suffice to permit the utilization of energy on energy-intensive endocrine functions, including reproduction. Falling leptin levels mediate the response to fasting; fasting decreases the amount of energy stored as triglyceride in fat cells, thus decreasing the amount of circulating leptin. This reduction in leptin receptor signaling therefore increases the drive to eat, increases hepatic glucose production (helping to support blood glucose levels during the fast), and diminishes the permissive action of leptin on endocrine function.

Mutation of the genes encoding leptin or its receptor promotes a similar response. In the absence of the leptin receptor signal in *db/db* mice, for instance, the brain cannot sense the leptin signal. This leads to increased appetite and decreased restraint on hepatic glucose production. The increase in appetite stimulates feeding, thereby expanding fat mass and leading to obesity, along with high leptin levels. In the absence of the leptin receptor, however, these elevated leptin levels cannot be sensed and so accomplish nothing. The lack of leptin-mediated restraint on hepatic glucose production in *db/db* mice also predisposes to diabetes—especially in the pres-

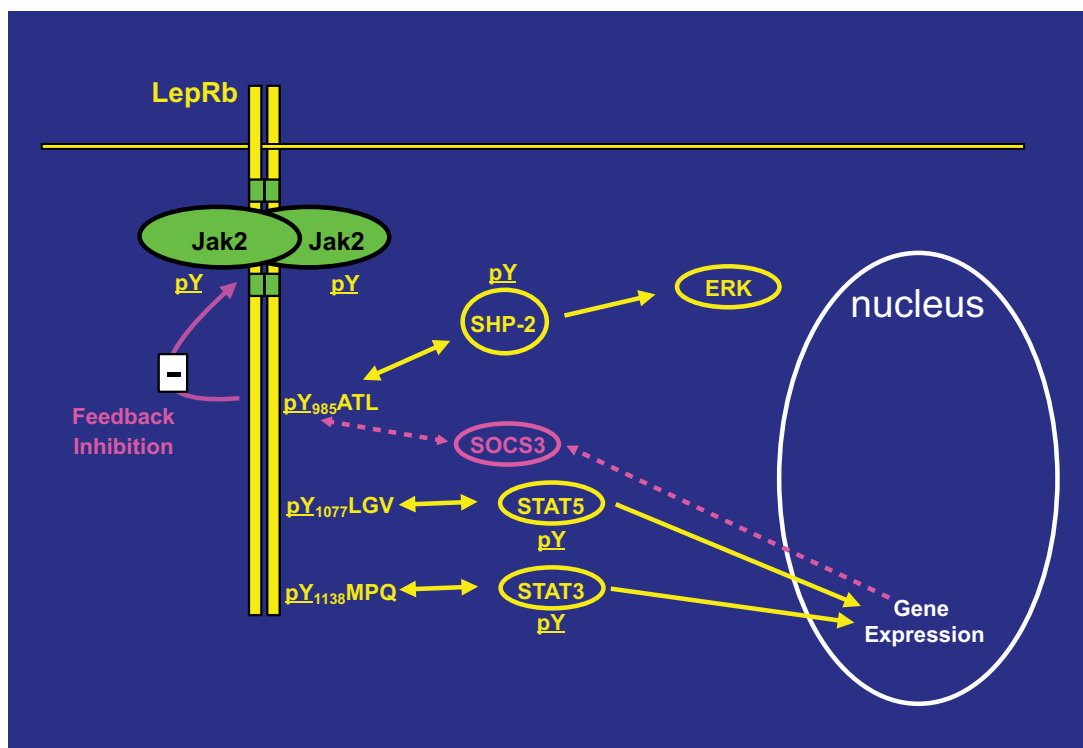


FIG. 1. Leptin receptor signaling pathways. Letters following phosphorylation sites represent subsequent amino acids, using the single-letter codes. See text for details.

ence of insulin resistance that goes hand in hand with obesity. The lack of leptin receptor signaling also decreases endocrine function, resulting in infertility and the disruption of other energy-requiring endocrine systems. The animal acts as though it is starved, even though fat stores are high, simply because it cannot perceive that the fat stores exist in the absence of leptin receptor signaling.

The central, overarching question that represents the focus of my laboratory is, how does leptin work? We are approaching this question in two ways. First, what are the cellular mechanisms of leptin receptor signaling and how do specific leptin receptor signals control energy balance and glucose homeostasis? Second, on what set or sets of neurons in the brain does leptin act to control energy balance and glucose homeostasis?

Because I was trained by Morris White, who received the Lilly Award in 1999 for his discoveries in cellular insulin receptor signaling, it was natural for my laboratory to follow the footsteps that Morris White had laid down in studying insulin signaling and to apply the same principles to the leptin receptor. This article does not show all of the data that helped us to work out these pathways; Fig. 1 summarizes the leptin receptor signaling pathways that our lab and others have worked out thus far, however.

The leptin receptor operates as a preformed dimer; it is an integral membrane protein with an extracellular hormone-binding domain and an intracellular signaling domain. The leptin receptor does not contain any intrinsic enzymatic activity, but relies on an associated tyrosine kinase (Jak2) for signaling. When leptin binds the receptor, it partially activates Jak2, which then autophosphorylates, further increasing the activity of the Jak2 kinase.

The fully activated Jak2 then phosphorylates three tyrosine residues on the intracellular domain of the leptin receptor. Each of these tyrosine residues lies in a distinct

amino acid motif and recruits a unique set of downstream signaling partners. Tyr1138 binds to a latent transcription factor STAT3, which is then phosphorylated by Jak2. Phosphorylated STAT3 translocates to the nucleus, where it controls gene expression. Tyr1077 recruits a similar transcription factor, STAT5, which is likewise phosphorylated and translocated to the nucleus to regulate the expression of other genes. Tyr985 binds to two proteins. First, it binds to SHP2, which also becomes tyrosine phosphorylated; this promotes the activation of the extracellular signal-related kinase (ERK) kinase signaling cascade. Second, STAT3 signaling increases the expression of a protein called the suppressor of cytokine signaling 3 (SOCS3), and SOCS3 binds to Tyr985. The binding of SOCS3 to Tyr985 inhibits Jak2, thus shutting down all of leptin receptor signaling in a process called “feedback inhibition.”

Hence, we regard the leptin receptor as having essentially four “inception” points from which spring specific downstream signals—Jak2, Tyr985 and SHP2/SOCS3, Tyr1077 and STAT5, and Tyr1138 and STAT3. Combined, these four signals mediate all of leptin action on energy balance, glucose homeostasis, and endocrine function.

Building upon this understanding of how the leptin receptor operates in the cell, we next set out to determine the role for each individual leptin receptor signal in leptin actions in intact animals. Our approach to this issue has been to mutate specific signaling sites on the leptin receptor and determine what the resultant mutant receptors can and cannot do when expressed in mice. By mutating a particular motif on the leptin receptor, we block a specific downstream signal; if we do this in an intact animal, we can study the animals to determine what the signal in question has to do with the regulation of physiology. For instance, if we mutate a signal that is

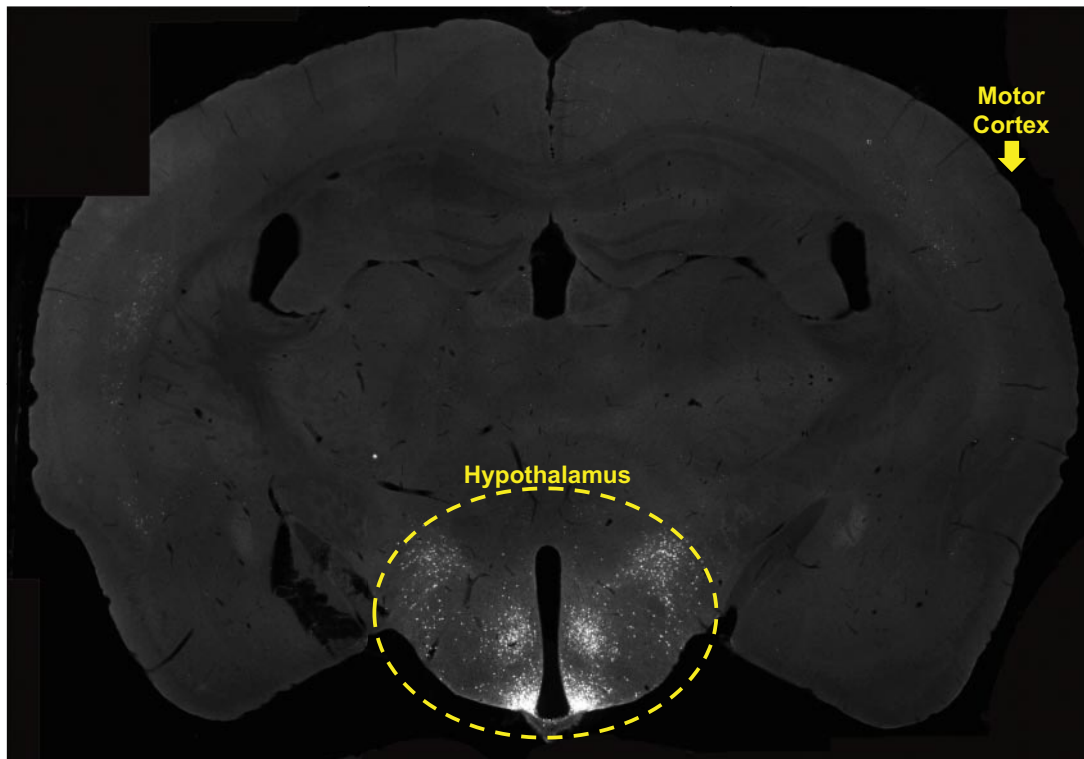


FIG. 2. Leptin receptor-expressing neurons in the mouse hypothalamus. Expression of green fluorescent protein (GFP) (shown in white) marks leptin receptor neurons in a coronal section of the brain of transgenic leptin receptor-GFP mice. Note the presence of multiple groups of leptin receptor neurons in the hypothalamus, but the presence of few leptin receptor neurons in other parts of the brain, including the motor cortex. (A high-quality digital representation of this figure is available in the online issue.)

crucial for the control of feeding and glucose homeostasis, we would expect that mice with this mutant receptor will be obese and diabetic.

In doing this, it is important to take into account that the leptin receptor is expressed only in a few select places in the brain. Figure 2 shows a cross-section of the mouse brain, with the leptin receptor-expressing cells shown in white. Leptin controls feeding but has little impact on volitional movement (such as wiggling your pinky finger), and while the leptin receptor is not expressed in the motor cortex, the brain area that controls motor function, it is expressed in the hypothalamus, although only in the subset of cells that have to do with energy balance and metabolism.

Because it is important that we express the mutant leptin receptors in the right places and at the right levels in the brain—that is, not in the motor cortex, but in the specific cells of the hypothalamus that express the leptin receptor—we decided to use a gene replacement strategy to put the mutant receptors into mice. Essentially, we swapped the mutant leptin receptor gene into the spot in the genome that is occupied by the endogenous leptin receptor gene. Thus, the mutant leptin receptor is expressed at the same levels and in the same neurons as the normal receptor would be in regular mice. Here, I discuss six types of mice, each expressing different variations on the leptin receptor (Fig. 3).

The first type is the normal animal, which we call wild type (WT). These mice have normal leptin receptors with the full complement of leptin receptor signals. We also have *db/db* mice, which possess a mutant leptin receptor that is missing all known signaling motifs, and thus cannot send any downstream signals.

Next, we have Delta/Delta mice that express what we call the delta receptor. This receptor is truncated right after the Jak2 interaction site and is missing all of the leptin receptor tyrosine phosphorylation sites. Thus, this receptor can signal via the receptor-associated Jak2 only. Additionally, we generated a series of mutant receptors that contain single point mutations, each of which disrupts a particular phosphorylation site and the downstream signals controlled by that site. In the first of these, we mutated Tyr985 to block the recruitment of SHP2 and SOCS3. In the second, we mutated Tyr1077 to block the recruitment of STAT5. The last of these contains a mutation of Tyr1138, thus blocking the binding of STAT3 to the leptin receptor.

The first set of studies discussed here is a comparison of normal, WT mice with *db/db* mice that have no leptin receptor and Delta/Delta mice whose leptin receptor signals by Jak2 only. We initially examined the body weight of these animals to determine whether Jak2 signaling alone could prevent obesity.

The body weights of the *db/db* and Delta/Delta animals are much higher than that of the WT animals, and the body weights are not different between the *db/db* and Delta/Delta animals. Similarly, the measurement of food intake in these animals reveals that the *db/db* and Delta/Delta animals eat similar amounts of food and that the amount they each consume is much greater than that for the WT animals. Consequently, while the WT animals have relatively low body fat, the *db/db* and Delta/Delta animals exhibit similarly elevated fat content; both are close to 50% body fat. These data suggest that Jak2 signaling alone, in the absence of other leptin receptor signals, cannot medi-

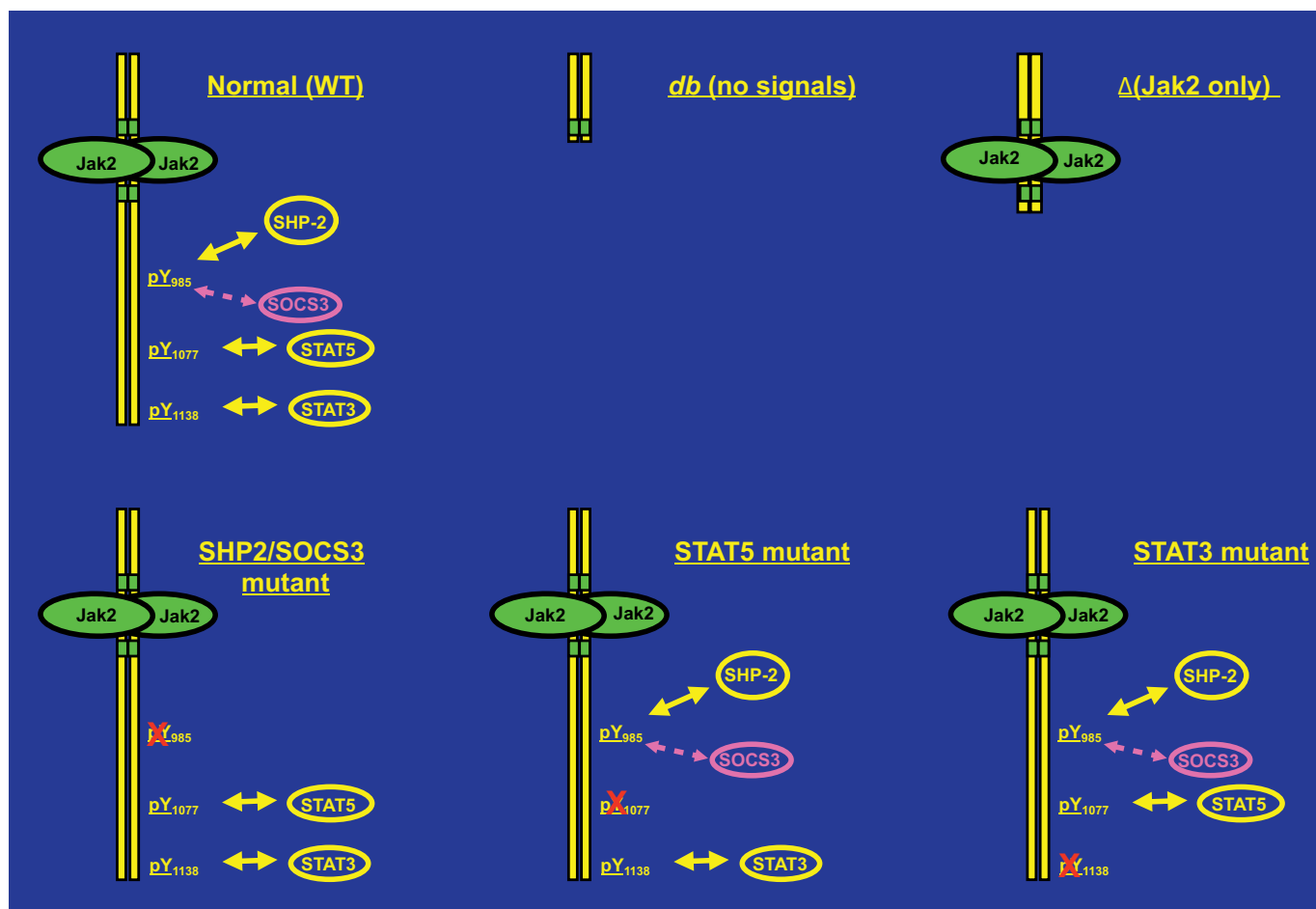


FIG. 3. Mutant leptin receptors expressed in mouse models. See text for details.

ate the leptin signal to control food intake and body weight.

What about glucose homeostasis? While blood glucose levels in the WT animals remain low for the duration of the study, the levels in the *db/db* mice are elevated even at very young ages. In contrast, the blood glucose levels in young Delta/Delta mice, although they are a bit higher than the normal animals, are lower than in the *db/db* mice. Overall, these data suggest that while Jak2 alone contributes little to the regulation of feeding and body weight, Jak2 signaling makes a modest contribution to the control of blood glucose levels.

Because the body weight and adiposity of the *db/db* and Delta/Delta animals are similar, the improvement in glucose homeostasis in the Delta/Delta relative to *db/db* mice represents a direct leptin effect, not a difference as a result of body fat levels. It is also important to note that Jak2 signaling alone is insufficient to mediate perfectly normal glucose homeostasis. This suggests that the tyrosine phosphorylation sites on the tail of the leptin receptor and the downstream signals that they control contribute importantly to the regulation of glucose homeostasis, in addition to mediating the effects of leptin on feeding and energy balance.

In order to determine the tyrosine phosphorylation site or sites on the tail of the leptin receptor that mediate these effects, we examined mice expressing single point mutations of the leptin receptor. The first of the mouse lines is mutant for Tyr985, and so this leptin receptor fails to recruit SHP2 and SOCS3.

What we found in these animals was essentially the opposite of a *db/db* animal. When eating a diet of normal mouse chow (this is the mouse diet equivalent of shredded wheat or kashi cereal), the mutant animals demonstrate a trend toward decreased body weight compared with the normal mice. Furthermore, if one feeds these animals a high-fat diet (this is similar to feeding them donuts or fast food), the WT animals crave this food, overeat, and gain a lot of weight. In contrast, the mutant animals gain relatively little weight. In fact, when one looks at food intake right after these animals are switched onto the high-fat diet, it turns out that the mutant animals eat substantially less of the high-fat food than the normal animals. These data suggest that, far from being compromised in their ability to respond to leptin, these mutant animals might actually be ultrasensitive to leptin.

To test this directly, we gave the mice a tiny amount of leptin over 3 days and followed their body weight. The amount of leptin that we used was so small that the WT animals lost essentially no weight. In contrast, the mutant animals lost 6–7% of their body weight over the 3-day treatment period. Additionally, glucose homeostasis is normal in this line of mutant animals.

Thus, the mice mutant for Tyr985 and SHP2/SOCS3 signaling exhibit no defects in the metabolic actions of leptin, suggesting that this residue does not play a role in mediating the effects of leptin on feeding and glucose homeostasis. In fact, these animals are actually more sensitive to leptin, suggesting that (similar to our findings in our initial signaling studies in cultured cells) Tyr985 acts

to inhibit the leptin receptor, decreasing leptin sensitivity. In addition, because Tyr985 is not doing much in this regard, the big guns of leptin receptor action on feeding and glucose homeostasis must be Tyr1077 and/or Tyr1138 and STAT3 and/or STAT5 signaling.

We thus examined the mice expressing the leptin receptor mutant for Tyr1077, which is impaired for STAT5 signaling. Compared with the WT animals, the STAT5 mutants tend to have a very small increase in body weight. Similarly, when we examine feeding, the trend line for the mutants lies very slightly above that for WT animals but is not significantly different. When we examine body fat, however, this more sensitive measure reveals a modest, but significant, increase in body fat in the STAT5 mutants compared with the WT mice. Thus, STAT5 plays a minor role in the regulation of body weight by leptin.

What about glucose homeostasis? In this case, there is no difference in blood glucose between the WT and mutant mice, and there is no significant difference in circulating insulin levels between the WT and mutant mice. In fact, even in an insulin tolerance test, which examines how sensitively the mice respond to insulin by testing the fall in glucose after insulin administration, the WT and mutant mice respond similarly.

All of these data reveal that Tyr1077 makes a very small contribution to the regulation of feeding and body fat, but is not required for the maintenance of normal glucose homeostasis. Thus, these data suggest that STAT3 signaling will be very important for the regulation of feeding, adiposity, and the regulation of glucose homeostasis.

In our final mutant leptin receptor, we disrupted Tyr1138, preventing the leptin receptor from engaging STAT3. From the very first time we saw these animals, it was clear that we had interfered with an important leptin signal. Figure 4 shows a picture of a 6-month-old leptin receptor-STAT3 signaling mutant mouse. This animal is very large and very interested in food. While a WT animal of this age would weigh about 30 g, this mouse weighs in at three and one-half times that much—over 108 g.

Comparing these animals more quantitatively with normal and *db/db* mice, one can see that the *db/db* animals weigh much more than the WT animals and that these STAT3 mutant animals weigh almost as much as the *db/db* animals. Furthermore, while the fat content of the WT animals is quite low, the *db/db* animals are almost 50% fat. The STAT3 mutant animals are also much fatter than the WT mice, almost as high in fat content as the *db/db* animals. These data suggest the following: 1) STAT3 signaling is very important for the regulation of body weight and adiposity, and 2) although STAT3 is important, it does not mediate 100% of leptin action because these mutant mice are not quite as heavy or overweight as the *db/db* animals.

In reference to food intake, the WT animals eat about 3.5 g of food per day, while the *db/db* and STAT3 mutant animals eat 6–7 g per day. Examining glucose homeostasis in these animals is complicated by the amount they eat and by their obesity as obesity promotes insulin resistance. Therefore, we not only examined blood glucose levels in the ad libitum fed animals, but also in the so-called pair-fed animals that were fed the amount of food eaten by the WT animals each day. The WT animals, of course, had normal blood glucose for the duration of the study. The *db/db* animals that were eating as much food as they liked displayed a very rapid increase in blood glucose levels. Mutant animals that lack STAT3 signaling also displayed

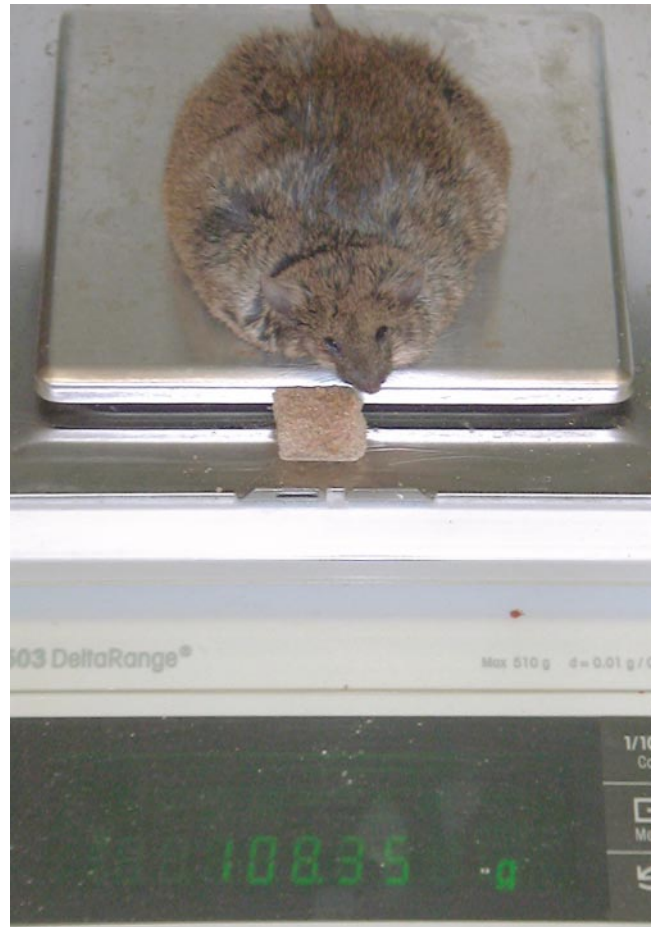


FIG. 4. Mouse mutant for leptin receptor Tyr1138.

an increase in blood glucose levels as they aged, although not nearly to the level of the *db/db* animals. The pair-fed *db/db* animals, which ate the same amount of food as the WT mice, demonstrated lower blood glucose than the freely feeding *db/db* animals—similar to the freely feeding STAT3 mutants. In contrast, if one pair feeds the STAT3 mutant animals, this normalizes their blood glucose.

These data show that Tyr1138→STAT3 signaling is very important for the regulation of feeding and also suggest that this signal is important for the regulation of glucose homeostasis, although a great deal of this effect of STAT3 on blood glucose is secondary to the control of feeding and adiposity. When these STAT3 mutant animals become obese, they also become insulin resistant, causing blood glucose levels to rise.

Overall the analysis of these mouse lines has revealed the intracellular signaling mechanisms by which the leptin receptor regulates whole body physiology. Jak2 makes a modest contribution to the regulation of glucose homeostasis; Tyr1138 and STAT3 signaling plays a crucial role in the regulation of feeding and adiposity and thereby the control of glucose homeostasis. Tyr1077 and STAT5 make a modest contribution to the regulation of feeding, and together STAT3 and STAT5 represent the major contributors to the regulation of energy homeostasis. In contrast, Tyr985 does not mediate important signals to suppress feeding and adiposity, but rather its major role in vivo is to mediate feedback inhibition, which limits leptin receptors signaling.

The next question we posed is, how do each of these

leptin receptor signals actually control feeding, glucose homeostasis, and the like? The main problem we face in addressing this question is essentially that the brain is not the liver. That is, although the liver is an essentially homogenous organ comprised of one major cell type, we cannot study leptin action in the brain as if all of the brain cells are the same.

Each type of brain cell is specialized, contains a distinct set of neurotransmitter chemicals, and communicates with only a few other brain cells to perform specific functions. As seen in Fig. 2, while the leptin receptor is not expressed everywhere in the brain, there are many different groups of leptin receptor expressing neurons in the brain—each of which presumably subserves a different function. Because we currently know very little about most of these leptin-responsive neurons, we need to determine the roles for each of these sets of neurons in leptin action.

This article also covers two different groups of leptin receptor-expressing neurons—the first of these lies in the lateral hypothalamic area (LHA). Why study the LHA? First, overeating and obesity represent major contributors to the onset of type 2 diabetes. Second, the LHA is known to regulate the mesolimbic dopamine system. The mesolimbic dopamine system is the part of the brain that regulates the desire for natural rewards (such as food and sex), along with artificial rewards, such as drugs of abuse. The seat of the mesolimbic dopamine system is a part of the brain called the ventral tegmental area (VTA), where lie a set of neurons that contain the neurotransmitter dopamine. Dopamine coming from these VTA neurons regulates “wanting” for rewarding things. The LHA interacts with the mesolimbic dopamine system to control feeding and drug taking. Therefore, we reasoned that the leptin receptor neurons in the LHA are poised to regulate an important participant in eating and overeating.

But is that what the lateral hypothalamic leptin receptor neurons actually do? To answer this question, Gina Leininger, a stellar postdoc in the lab, performed an experiment where she administered a very small amount of leptin directly into the LHA of the *ob/ob* mice, so that these were the only neurons in the brain that would respond to the leptin. This small dose of leptin decreased the amount of food that the mice ate and decreased their body weight over 24 h.

We also looked to see what was happening in the brain of these *ob/ob* animals following the administration of leptin into the LHA. Now, since we were only administering the leptin on one side of the brain, we would only expect to see one side of the brain responding to the leptin. Indeed, leptin increased the expression of tyrosine hydroxylase (the enzyme that makes dopamine) and increased the amount of dopamine in the mesolimbic system, but only on the side of the brain that received leptin. Thus, leptin acts on the LHA leptin receptor neurons, which we have shown to project to the VTA, thereby regulating the amount of dopamine in the mesolimbic dopamine system and contributing to the control of feeding and body weight.

The next and final area that I discuss here is a part of the hypothalamus called the ventral premammillary nucleus (PMv). In this case, we chose to study this region because it contains a very large number of leptin receptor neurons, and we reasoned it must be important if there are so many leptin responsive neurons. Other interesting things about the PMv include that it is sexually dimorphic—there are

differences in the neurons between male and female mice. Indeed, the PMv in male mice expresses the testosterone receptor, and it projects more strongly in male than in female mice to a part of the brain called the paraventricular nucleus of the hypothalamus (PVH). The PVH, although it contains only few leptin receptor neurons, is a major site for controlling food intake and metabolism.

We thus hypothesized that PMv leptin receptor neurons would be important for the control of energy balance and glucose homeostasis and that it would be more important for these things in male than in female mice. This suggested an experiment to remove the leptin receptor from the PMv and see what happens to obesity and diabetes in male and female mice. So that is exactly what Rebecca Leshan, a superb graduate student in my lab, did. Compared with the WT animals, *db/db* female mice have a very high body weight. The animals lacking leptin receptor in the PMv only (PMvKO mice) also have increased body weight compared with that in normal controls, but their body weight is not as great as that seen for the *db/db* female mice.

Compared with the WT males, the *db/db* male mice also demonstrate increased body weight. In this case, however, the PMvKO male mice have body weights indistinguishable from those of the *db/db* male mice. Similarly, food intake is dramatically increased in the *db/db* female mice compared with the WT animals, and although it is higher in the PMvKO female mice than in the controls, these mice eat far less than the *db/db* female mice. Again, in the male mice, food intake in the PMvKO mice is higher than in the control animals, but the PMvKO male mice eat as much food as the *db/db* mice that have no leptin receptor anywhere in the brain.

What about glucose homeostasis? Blood glucose is normal in the WT female mice and elevated in the *db/db* female mice, but there is little increase in blood glucose in the female PMvKO animals. Once again, the male mice are a different story: blood glucose levels are elevated in the *db/db* male compared with normal animals, and the PMvKO male mice exhibit similarly elevated blood glucose levels. As for glucose, insulin levels in the PMvKO female mice are somewhat elevated, suggesting some insulin resistance, but they remain far below the levels seen in the *db/db* female mice. However, in male mice, insulin levels are similarly elevated in the PMv knockout and *db/db* male mice.

Together, these data demonstrate that leptin action via PMv leptin receptor neurons in the male mice is crucial to the regulation of food intake, body weight, and glucose homeostasis. In the female mice, on the other hand, the PMv contributes to each of these aspects of food intake, body weight, and glucose metabolism, but to a much lesser extent than in the male mice. What might then leptin action via the PMv leptin receptor neurons be doing in the female mice? Earlier, I mentioned that leptin is an important regulator of endocrine function, and one of the endocrine functions that leptin controls is fertility. As it turns out, there is a major defect in reproductive function in the PMvKO female mice. Rebecca Leshan examined the onset of puberty in these animals and found that essentially all WT animals enter puberty by the time they are 50 or 60 days old; in contrast, the PMvKO female mice enter puberty at a much slower rate, and almost 75% of them fail to enter full puberty at all.

Thus, the leptin receptor neurons in the male and female PMv perform somewhat overlapping but somewhat dis-

tinct functions: in male mice, these neurons play a dominant role in the regulation of metabolism, while in female mice, the role these neurons play in the regulation of body weight and glucose homeostasis is more minor, and these neurons play a major role in the regulation of fertility.

We have only begun to scratch the surface: there is a lot more work to be done in the system because there are many different types of leptin receptor neurons in places that we and others have only just begun to think about. For each of these sets of neurons, we need to determine what brain areas they control, what neurotransmitters they use, and how they contribute to energy balance and glucose homeostasis—just as we have done for the LHA and the PMv. We also need to understand the roles for specific leptin receptor signals in the regulation of each of these neuronal populations and to contemplate how these neurons and the specific signals that control them might be targeted for the therapy of obesity and type 2 diabetes.

ACKNOWLEDGMENTS

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stand on the shoulders of giants. This saying has several meanings at each of multiple levels: First, without the contributions of those who came before us and who work around us, none of our work would be possible. The second meaning of this phrase refers to mentorship, which has multiple dimensions. In my case, it includes a pantheon of spectacular colleagues who have discussed, advised, and provided constructive criticism throughout my career. I would also like to thank Ron Kahn, who provided me with the opportunity to establish my independence when I began working on leptin at the Joslin Diabetes Center, and Peter Arvan, my incredibly energetic and continuously supportive chief at the University of Michigan. For many of us, there are also those special individuals who dedicate the time and devote the energy to shape our thinking, guide our sense of ethics, and nurture our development as scientists in a particularly close way. In my case, I was extraordinarily fortunate to have been trained in the laboratory of Morris White, who has been and continues to be a spectacular mentor. Finally, I would like to thank my family. I am incredibly fortunate to enjoy the love and support of this wonderful group of people. My parents, Beverly and Martin Myers, have supported and encouraged me throughout my life. My wife, Diane Fingar, is a superb researcher in her own right. I thank her not only for supporting my career decisions and tolerating my idiosyncrasies but also for her critical scientific insights along the way. We are lucky to have two wonderful boys, Graham and Lee, who largely tolerate our eccentricities, but who also keep us grounded and aware of our boundaries.

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