



## Diabetes, Obesity, and the Brain

Michael W. Schwartz, *et al.*

*Science* **307**, 375 (2005);

DOI: 10.1126/science.1104344

**The following resources related to this article are available online at [www.sciencemag.org](http://www.sciencemag.org) (this information is current as of January 17, 2007):**

**Updated information and services**, including high-resolution figures, can be found in the online version of this article at:

<http://www.sciencemag.org/cgi/content/full/307/5708/375>

A list of selected additional articles on the Science Web sites **related to this article** can be found at:

<http://www.sciencemag.org/cgi/content/full/307/5708/375#related-content>

This article **cites 50 articles**, 28 of which can be accessed for free:

<http://www.sciencemag.org/cgi/content/full/307/5708/375#otherarticles>

This article has been **cited by** 66 article(s) on the ISI Web of Science.

This article has been **cited by** 36 articles hosted by HighWire Press; see:

<http://www.sciencemag.org/cgi/content/full/307/5708/375#otherarticles>

This article appears in the following **subject collections**:

Medicine, Diseases

<http://www.sciencemag.org/cgi/collection/medicine>

Information about obtaining **reprints** of this article or about obtaining **permission to reproduce this article** in whole or in part can be found at:

<http://www.sciencemag.org/help/about/permissions.dtl>

Why is obesity an inflammatory state and why does inflammation cause diabetes? The search for answers to these questions takes us again to evolutionary considerations. Perhaps the response to infection is more effective when glucose is shunted from muscle to the inflammatory cells involved in the immune response and tissue repair (46). A potentially unifying view is that the body's ability to survive major stress, including infection and starvation, is enhanced by peripheral insulin resistance that preserves the brain's glucose supply (47). This hypothesis might explain why cortisol, the major stress hormone, causes insulin resistance and stimulates the innate immune response (31), even though chronic cortisol exposure is anti-inflammatory because of down-modulation of the acquired immune response. The stress connection may extend to individual cells, as it has recently been shown that intracellular stress induces insulin resistance in a manner that is exacerbated by obesity, potentially through adipocyte-secreted factors (48). Moreover, chronic metabolic stress impairs the ability of pancreatic beta cells to secrete sufficient insulin to overcome insulin resistance, which is a hallmark of type 2 diabetes (49).

### Not a Tall Tale: How Will it End?

Humanity has been curious about the giraffe's long neck since time immemorial. Although it is very likely that this unusual phenotype contributed to the survival of that species, there is as yet no molecular or genetic explanation for it. We are now curious about the explanation for the dramatic rise in human obesity and diabetes. It is interesting to speculate about the origin of genes that make us particularly susceptible to these metabolic diseases in the setting of

modern lifestyles. The theories that emerge may provide clues to the underlying mechanisms, especially if they can be supported by studies in model organisms (50). Of course, natural selection itself has the potential to solve these health crises, but only when they threaten the survival of our species. A more optimistic view is that we can turn the tide of these epidemics by focusing on mechanistic questions such as how obesity causes diabetes. It is hoped that harnessing this knowledge will allow us to successfully intervene before natural selection takes over.

### References and Notes

1. A. H. Mokdad et al., *JAMA* **289**, 76 (2003).
2. W. H. Dietz, *N. Engl. J. Med.* **350**, 855 (2004).
3. P. Hogan, T. Dall, P. Nikolov, *Diabetes Care* **26**, 917 (2003).
4. K. M. Narayan, J. P. Boyle, T. J. Thompson, S. W. Sorensen, D. F. Williamson, *JAMA* **290**, 1884 (2003).
5. S. J. Gould, *Nat. Hist.* **5**, 18 (1996).
6. E. E. Calle, M. J. Thun, J. M. Petrelli, C. Rodriguez, C. W. Heath Jr., *N. Engl. J. Med.* **341**, 1097 (1999).
7. P. Zimmet, C. R. Thomas, *J. Intern. Med.* **254**, 114 (2003).
8. J. V. Neel, *Am. J. Hum. Genet.* **14**, 353 (1962).
9. S. O'Rahilly, I. S. Farooqi, G. S. Yeo, B. G. Challis, *Endocrinology* **144**, 3757 (2003).
10. J. Diamond, *Nature* **423**, 599 (2003).
11. C. M. Damcott, P. Sack, A. R. Shuldiner, *Endocrinol. Metab. Clin. North Am.* **32**, 761 (2003).
12. R. H. Unger, *Trends Endocrinol. Metab.* **14**, 398 (2003).
13. J. M. Friedman, *Nutr. Rev.* **60**, S1 (2002).
14. I. S. Farooqi et al., *Nature* **414**, 34 (2001).
15. I. Shimomura, R. E. Hammer, S. Ikemoto, M. S. Brown, J. L. Goldstein, *Nature* **401**, 73 (1999).
16. E. A. Oral et al., *N. Engl. J. Med.* **346**, 570 (2002).
17. C. K. Welt et al., *N. Engl. J. Med.* **351**, 987 (2004).
18. R. E. Frisch, J. W. McArthur, *Science* **185**, 949 (1974).
19. C. N. Hales, D. J. Barker, *Diabetologia* **35**, 595 (1992).
20. T. Jenuwein, C. D. Allis, *Science* **293**, 1074 (2001).
21. G. Blander, L. Guarente, *Annu. Rev. Biochem.* **73**, 417 (2004).
22. E. E. Kershaw, J. S. Flier, *J. Clin. Endocrinol. Metab.* **89**, 2548 (2004).
23. M. Das, I. Gabriely, N. Barzilay, *Obes. Rev.* **5**, 13 (2004).
24. C. Weyer et al., *Mol. Genet. Metab.* **72**, 231 (2001).
25. E. D. Abel et al., *Nature* **409**, 729 (2001).
26. H. Masuzaki et al., *Science* **294**, 2166 (2001).
27. R. N. Bergman, M. Ader, *Trends Endocrinol. Metab.* **11**, 351 (2000).
28. G. Boden, G. I. Shulman, *Eur. J. Clin. Invest.* **32** (suppl. 3), 14 (2002).
29. M. W. Rajala, P. E. Scherer, *Endocrinology* **144**, 3765 (2003).
30. M. Haluzik, J. Parizkova, M. M. Haluzik, *Physiol. Res.* **53**, 123 (2004).
31. C. Gabay, I. Kushner, *N. Engl. J. Med.* **340**, 448 (1999).
32. H. Shi, I. Tzameli, C. Bjorbaek, J. S. Flier, *J. Biol. Chem.* **279**, 34733 (2004).
33. S. M. Rangwala, M. A. Lazar, *Trends Pharmacol. Sci.* **25**, 331 (2004).
34. J. Auwerx, *Diabetologia* **42**, 1033 (1999).
35. H. Xu et al., *J. Clin. Invest.* **112**, 1821 (2003).
36. S. P. Weisberg et al., *J. Clin. Invest.* **112**, 1796 (2003).
37. M. W. Rajala et al., *Diabetes* **53**, 1671 (2004).
38. H. Osawa et al., *Am. J. Hum. Genet.* **75**, 678 (2004).
39. C. M. Steppan et al., *Nature* **409**, 307 (2001).
40. L. Patel et al., *Biochem. Biophys. Res. Commun.* **300**, 472 (2003).
41. E. Ottaviani, C. Franceschi, *Domest. Anim. Endocrinol.* **15**, 291 (1998).
42. G. S. Hotamisligil, *Int. J. Obes. Relat. Metab. Disord.* **27** (suppl. 3), S53 (2003).
43. A. O. Agwunobi, C. Reid, P. Maycock, R. A. Little, G. L. Carlson, *J. Clin. Endocrinol. Metab.* **85**, 3770 (2000).
44. G. Van den Berghe, *J. Clin. Invest.* **114**, 1187 (2004).
45. M. Yuan et al., *Science* **293**, 1673 (2001).
46. J. M. Fernandez-Real, W. Ricart, *Diabetologia* **42**, 1367 (1999).
47. P. H. Black, *Brain Behav. Immun.* **17**, 350 (2003).
48. U. Ozcan et al., *Science* **306**, 457 (2004).
49. C. J. Rhodes, *Science*, **307**, 380.
50. V. D. Longo, C. E. Finch, *Science* **299**, 1342 (2003).
51. A. Fukuhara et al., *Science* **307**, 426 (2005).
52. I thank R. Ahima, M. Birnbaum, M. Brown, A. Lazar, S. Mandel, and A. Rubenstein for critical comments on the manuscript and members of my laboratory for helpful discussions. I apologize that many relevant articles could not be cited because of space limitations. Supported by the National Institute of Diabetes, Digestive, and Kidney Diseases.

10.1126/science.1104342

### VIEWPOINT

## Diabetes, Obesity, and the Brain

Michael W. Schwartz<sup>1,2\*</sup> and Daniel Porte Jr.<sup>1,3,4</sup>

Recent evidence suggests a key role for the brain in the control of both body fat content and glucose metabolism. Neuronal systems that regulate energy intake, energy expenditure, and endogenous glucose production sense and respond to input from hormonal and nutrient-related signals that convey information regarding both body energy stores and current energy availability. In response to this input, adaptive changes occur that promote energy homeostasis and the maintenance of blood glucose levels in the normal range. Defects in this control system are implicated in the link between obesity and type 2 diabetes.

More than a century ago, the renowned physiologist Claude Bernard observed that diabetes could be induced in animals by puncture of the floor of the fourth cerebral ventricle ("pique diabetique") (1). Although this striking finding suggested a key role for

the brain in glucose homeostasis, its importance was largely neglected after the discovery of insulin in 1923. However, new findings have revived interest in the role played by the brain in both glucose homeostasis and the mechanism linking obesity to type

2 diabetes. As Bernard might have predicted, this new information suggests that a full understanding of the pathogenesis of these disorders must incorporate a role for the brain in metabolic regulation.

<sup>1</sup>Division of Metabolism, Endocrinology and Nutrition, University of Washington, Seattle, WA 98110, USA. <sup>2</sup>Harborview Medical Center, 325 Ninth Avenue, Seattle, WA 98110, USA. <sup>3</sup>Division of Metabolism, Diabetes and Endocrinology, University of California San Diego, San Diego, CA 92161, USA. <sup>4</sup>Division of Metabolism, Diabetes and Endocrinology, VA San Diego Health Care System, 3350 La Jolla Village Drive, San Diego, CA 92161, USA.

\*To whom correspondence should be addressed. E-mail: mschwartz@u.washington.edu

Evidence now indicates that the brain processes information from “adiposity signals” such as the hormones insulin and leptin, which circulate in proportion to body fat mass, and integrates this input with signals from nutrients such as free fatty acids (FFAs). In response, feeding behavior, autonomic outflow, and substrate metabolism are adjusted in ways that promote homeostasis of both energy stores and fuel metabolism. The overarching hypothesis is that in times of plenty (ample fat stores and food availability), input to key brain areas from these afferent signals leads to inhibition of both energy intake and endogenous glucose production, while simultaneously increasing energy expenditure and mobilizing fat stores (Fig. 1) (2, 3). The net effect is that when the brain senses that body energy content and nutrient availability are sufficient, further increases of stored energy (in the form of fat) and circulating nutrients (such as glucose) are resisted.

Conversely, a decrease in neuronal input from one or more of these afferent signals is proposed to alert the brain to a current or pending deficiency of stored energy or nutrient availability. In turn, the brain activates responses that promote positive energy balance (increased food intake and decreased energy expenditure) and raise circulating nutrient levels (increased hepatic glucose production). As body fat content and plasma glucose levels begin to increase, circulating concentrations of leptin, insulin, and FFAs increase as well. The latter are sensed in the brain, favoring the return of food intake and glucose production to their original values. The central nervous system (CNS) response to these signals is therefore catabolic in nature and is in direct opposition to the anabolic actions of insulin and FFAs on fuel storage and metabolism in peripheral tissues. Should defects arise in the CNS response to these signals, the resulting imbalance in this homeostatic system will result in elevated levels of both body fat content and hepatic glucose production. Accordingly, reduced secretion of, sensing of, or responsiveness to afferent hormonal or nutrient-related signals can be predicted to cause weight gain and insulin resistance: car-

dinal features that link obesity with type 2 diabetes.

### The Brain as an Insulin-Sensitive Tissue

In contrast to its prominent action in liver, muscle, and fat, insulin is not a major regulator of glucose use by the brain (4). This observation, combined with the widespread belief that a peptide the size of insulin would be unable to cross the blood-brain barrier, has led to the perception of the brain as an insulin-insensitive tissue. Recent observations have revealed this presumption to be erroneous and demonstrate that even though the brain is insulin-independent (with respect to glucose use), it clearly is not insulin-insensitive.

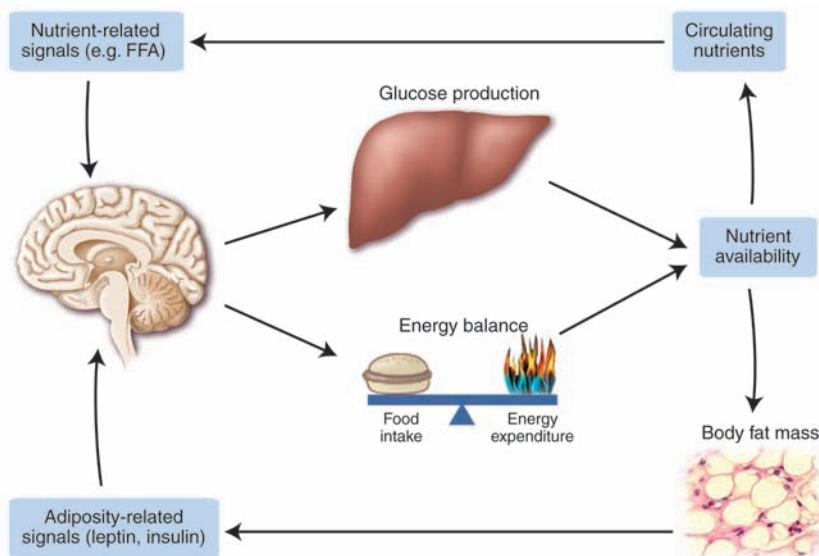
Evidence of insulin action in the brain emerged 25 years ago with the demonstra-

tion of insulin action in the brain (5). Evidence of insulin action in the brain emerged 25 years ago with the demonstra-

tion of insulin action in the brain (5). Evidence of insulin action in the brain emerged 25 years ago with the demonstra-

tion of insulin action in the brain (5). Evidence of insulin action in the brain emerged 25 years ago with the demonstra-

tion of insulin action in the brain (5). Evidence of insulin action in the brain emerged 25 years ago with the demonstra-



**Fig. 1.** Model depicting the control of energy homeostasis and hepatic glucose metabolism by adiposity- and nutrient-related signals. Neuronal systems sense and respond to input from hormones such as insulin and leptin that are secreted in proportion to body energy stores and from the metabolism of circulating nutrients (such as glucose and FFAs). In response to this input, adaptive changes occur in energy intake, energy expenditure, and hepatic glucose production.

tion in a primate model that food intake decreases when a low dose of insulin is delivered directly to the brain by continuous intracerebroventricular (icv) infusion (5). When this fact was combined with evidence that insulin circulates at levels proportionate to body fat mass, that circulating insulin is transported into the brain, and that insulin receptors are concentrated in brain areas involved in the control of food intake and autonomic function (6), insulin emerged as a candidate “adiposity negative feedback” signal in the central control of energy homeostasis. When it was later shown that icv insulin administration also reduces hepatic glucose production (by increasing

heightened significance in view of evidence that IRS-PI3K signal transduction in hypothalamic neurons is also activated by the adipocyte hormone leptin (14), and that deletion of IRS2 from hypothalamic neurons results in obesity and insulin resistance (15, 16).

### Leptin and Glucose Homeostasis

The neuronal response to leptin receptor activation involves the Janus kinase–signal transducer and activator of transcription (Jak-STAT) pathway (17). Among the proteins induced by leptin-mediated STAT signaling is suppressor of cytokine signaling-3 (SOCS3), which inhibits leptin activation of the Jak-STAT pathway (17). Interestingly, SOCS3 also potently inhibits signaling by insulin receptors (18), and sensitivity to both insulin and leptin is augmented in mice with reduced neuronal expression of SOCS3 (19, 20). That these mice are protected against diet-induced obesity suggests further that SOCS3-mediated attenuation of the neuronal response to adiposity signals is required for weight gain induced by consumption of a highly palatable, energy-rich diet. Combined with evidence that both leptin- and insulin-induced signaling involves the IRS-PI3K pathway, the cellular actions of these two adiposity-related hormones appear to overlap at multiple levels within neuronal systems that are important to both energy homeostasis and glucose metabolism (21).

Genetic leptin deficiency in *ob/ob* mice (22) is associated not only with pronounced hyperphagia and obesity but with insulin resistance and mild-to-moderate diabetes. Although impaired glucose metabolism in these mice is clearly driven by their severe obesity, leptin deficiency per se appears to make an independent contribution, because the glucose-lowering effect of leptin occurs at doses below those needed to reverse obesity (23) and cannot be reproduced by simple caloric restriction (24). In addition, the hyperglycemic consequences of impaired leptin signaling are dependent on co-existent defects in insulin secretion that are, at least in part, genetically determined. Background genes that influence endocrine pancreatic function are therefore important determinants of the predisposition to diabetes in genetic models of deficient leptin signaling. The lack of such genes may explain why children with genetic leptin deficiency are not reported to have diabetes, although they are severely obese (25).

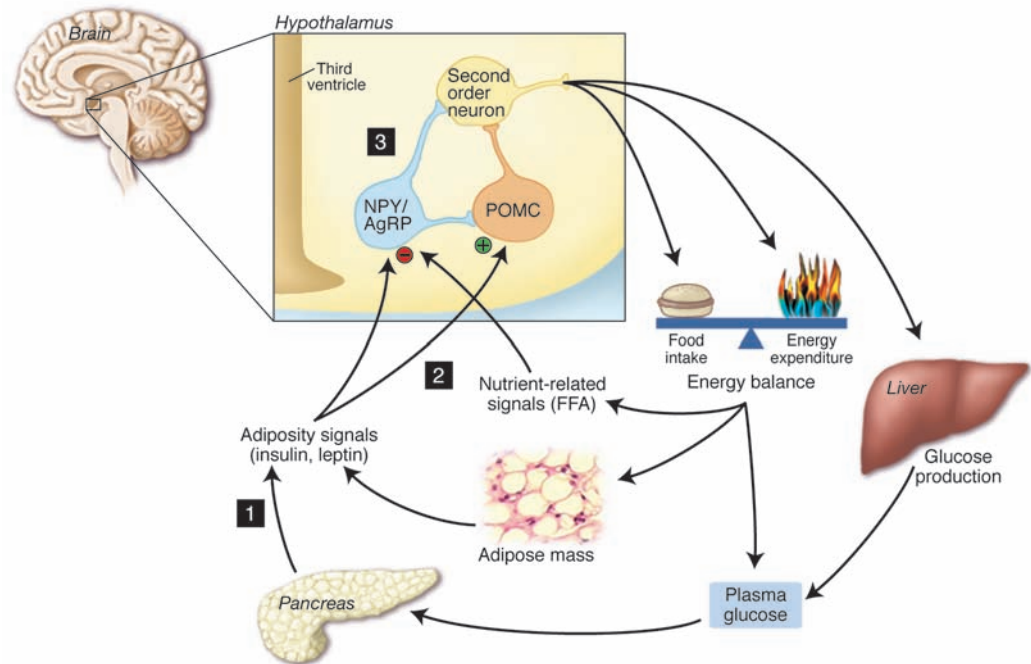
A variety of gene defects have been identified that disrupt adipogenesis, causing a disorder known as lipodystrophy that is characterized by a loss of body adipose tissue, leptin deficiency, and a unique and severe form of insulin resistance and diabetes (26). Mouse models recapitulate the key features of the human disorder and have yielded substantial new insights into both its metabolic basis and its treatment (27). Because lipodystrophic mice are lean and, by definition, have reduced or absent fat mass, their body weight phenotype contrasts sharply with the severe obesity of *ob/ob* mice. Yet lipodystrophic and leptin-deficient mice share key features in common, including hyperphagia, insulin resistance, diabetes, and markedly reduced leptin signaling. Because the diabetes phenotype of lipodystrophic and leptin-deficient mice is ameliorated by leptin administration (28), a role for leptin deficiency in both diabetes syndromes is suggested (29). Moreover, icv administration of leptin at a low dose reversed the metabolic disturbance of lipodystrophic mice as effectively as systemic administration of a much higher dose (30), suggesting that the antidiabetic effect of leptin in this setting involves an action in the brain.

Lipodystrophic diabetes also develops in mice that express insulin receptors in the liver and pancreas but otherwise lack the insulin receptor gene (8). Surprisingly, this lipodystrophy is prevented by the expression of insulin receptors in the brain, in addition

to the liver and pancreas (8). How might insulin action in the brain affect the predisposition to lipodystrophy? One possibility is suggested by the recently discovered mutations of the *BSCL2* gene. Although the function of the protein encoded by this gene (termed “seipin”) remains to be determined, these mutations are responsible for one variant of the Berardinelli-Seip congenital lipodystrophy syndrome associated with mental retardation in humans (31, 32). This gene is highly expressed in the brain but only modestly in adipocytes (31), suggesting a role for the CNS in the pathogenesis of lipodystrophy in humans.

### Hypothalamic Targets of Insulin and Leptin Action

The arcuate nucleus, situated adjacent to the floor of the third ventricle in the mediobasal hypothalamus, contains neurons that exert potent effects on food intake, energy expenditure, and glucose homeostasis and are regulated by input from both hormonal and nutrient-related signals (2, 33). “Anabolic” neurons coexpress neuropeptide Y (NPY) and Agouti-related peptide (AgRP), two peptides that potently stimulate food intake and reduce energy expenditure, and thereby promote weight gain (34–36). These neurons are inhibited by leptin and insulin (33); consequently, reduced neuronal input from these hormones increases hypothalamic signaling by both peptides. Central administration of NPY causes insulin resistance and



**Fig. 2.** Neurocentric model depicting sites where defects in the negative feedback regulation of energy balance and glucose production predispose to weight gain and insulin resistance. Defects in the secretion of insulin or leptin (1), in the hypothalamic sensing of adiposity- or nutrient related signals (2), or in the neuronal responsiveness to these inputs (3) predispose to both positive energy balance and increased glucose production. If sustained, these will result in pathological weight gain and insulin resistance.



arises from an excess of body fat. If pancreatic  $\beta$  cells cannot appropriately increase insulin secretion, glucose intolerance and ultimately frank hyperglycemia ensue. These same observations, however, are compatible with an alternative, neurocentric model (Fig. 3). This model is predicated on four key observations highlighted in this essay. First, the brain is not insulin-insensitive; on the contrary, it uses input from insulin, leptin, and nutrient-related signals to regulate both body fat content and hepatic insulin sensitivity (Fig. 2). Second, impaired neuronal signaling by these afferent signals causes hyperphagia, weight gain, and hepatic insulin resistance through mechanisms that are at least partly independent of one another. Third, obesity is strongly associated with biochemical resistance to both insulin and leptin. Fourth, defective insulin secretion (which presumably reduces insulin delivery to the brain as well as to other tissues) is a prerequisite for type 2 diabetes (54). Together these observations support a model in which reduced neuronal insulin and leptin signaling contributes to the link between excess body fat and disordered glucose metabolism.

According to this model, obesity and impaired glucose metabolism can be predicted to arise from any of several defects that affect how the brain receives or processes input from key adiposity- or nutrient-related signals. Reduced insulin secretion can be invoked as a primary event, because reduced insulin delivery to the brain favors both weight gain and hepatic insulin resistance. As obesity progresses, a further deterioration of insulin sensitivity occurs (due to increased body fat content) that, together with impaired insulin secretion, will cause plasma glucose levels to increase. Although such increases may initially be limited by a compensatory increase of insulin secretion, the ability of the  $\beta$  cell to meet the demand posed by progressive weight gain and insulin resistance may ultimately reach its limit, leading to overt hyperglycemia. If obesity causes resistance to insulin in neurons as well as in peripheral tissues, a vicious cycle is created that accelerates weight gain and hepatic insulin resistance and thereby hastens diabetes onset (Fig. 3).

Defects in either the neuronal sensing of, or response to, afferent hormonal or nutrient-related signals can also set in motion a pathological cascade that progresses ultimately to obesity and diabetes. Because convergent signal transduction (for example, via the IRS-PI3K signaling pathway) and termination (for example, SOCS3) mechanisms mediate the neuronal actions of insulin and leptin, defects within a single biochemical pathway can potentially cause

resistance to the central actions of both hormones (21). This in turn can be predicted to induce hyperphagia, weight gain, hepatic insulin resistance, and glucose intolerance. The feasibility of this concept is strengthened by evidence implicating impaired IRS-PI3K signal transduction in the insulin resistance of peripheral tissues in diabetic humans and animal models (13). When combined with a  $\beta$ -cell defect, a feed-forward mechanism is again set in motion whereby reduced insulin and leptin action in the brain and periphery initially favors weight gain and insulin resistance, progressing to glucose intolerance and ultimately diabetes. Because functional resistance to both leptin and insulin is common among the obese, this hypothesis warrants careful consideration (21) (Fig. 3).

Direct evidence in support of these predictions was recently provided from studies of mice in which IRS2 was selectively deleted from pancreatic  $\beta$  cells and hypothalamic neurons (15, 16). Because IRS-2 is necessary for  $\beta$ -cell survival, a gradual, progressive loss of  $\beta$ -cell mass occurs in these mice and predisposes them to diabetes. Because IRS-2 is also implicated in neuronal signaling by insulin and leptin, deletion of this protein from the hypothalamus impairs afferent input from the two known adiposity signals. Consequently, these animals develop obesity and insulin resistance that, combined with  $\beta$ -cell dysfunction, progress to glucose intolerance and finally to diabetes. Disruption of signaling via the IRS-PI3K pathway is therefore sufficient to cause obesity and diabetes, even when this defect is limited to only the brain and pancreas.

A neurocentric model to explain the link between obesity and diabetes also predicts that the risk of these disorders is strongly increased by environmental factors that favor weight gain (such as an abundance of highly palatable, energy-dense foods combined with a minimal requirement for physical activity). Accordingly, therapies that restore neuronal signaling by key afferent signals may prove beneficial for both obesity and diabetes, especially when combined with adjustments in diet and physical activity. Therefore, as Bernard anticipated in 1854, progress in understanding and treating diabetes will require an improved understanding of brain systems that control body fuel homeostasis and energy storage.

#### References and Notes

1. C. Bernard, *Leçons de physiologie expérimentale appliquées à la médecine* (Bailliere et Fils, Paris, 1854).
2. R. J. Seeley, S. C. Woods, *Nature Rev. Neurosci.* **4**, 901 (2003).

3. S. Obici, Z. Feng, A. Arduini, R. Conti, L. Rossetti, *Nature Med.* **9**, 756 (2003).
4. E. R. Seaquist, G. S. Damberg, I. Tkac, R. Gruetter, *Diabetes* **50**, 2203 (2001).
5. S. C. Woods, E. C. Lotter, L. D. McKay, D. Porte Jr., *Nature* **282**, 503 (1979).
6. M. W. Schwartz, D. P. Figlewicz, D. G. Baskin, S. C. Woods, D. Porte Jr., *Endocr. Rev.* **13**, 387 (1992).
7. S. Obici, B. B. Zhang, G. Karkanas, L. Rossetti, *Nature Med.* **8**, 1376 (2002).
8. H. Okamoto, J. Nakae, T. Kitamura, B. C. Park, I. Dragatsis, D. Accili, *J. Clin. Invest.* **114**, 214 (2004).
9. S. Obici, Z. Feng, G. Karkanas, D. G. Baskin, L. Rossetti, *Nature Neurosci.* **5**, 566 (2002).
10. J. C. Bruning et al., *Science* **289**, 2122 (2000).
11. M. F. White, *Science* **302**, 1710 (2003).
12. K. D. Niswender et al., *Diabetes* **52**, 227 (2003).
13. G. I. Shulman, *J. Clin. Invest.* **106**, 171 (2000).
14. K. D. Niswender et al., *Nature* **413**, 794 (2001).
15. N. Kubota et al., *J. Clin. Invest.* **114**, 917 (2004).
16. X. Lin et al., *J. Clin. Invest.* **114**, 908 (2004).
17. S. H. Bates, M. G. Myers, *J. Mol. Med.* **82**, 12 (2004).
18. K. Ueki, T. Kondo, C. R. Kahn, *Mol. Cell Biol.* **24**, 5434 (2004).
19. J. K. Howard et al., *Nature Med.* **10**, 734 (2004).
20. H. Mori et al., *Nature Med.* **10**, 739 (2004).
21. M. W. Schwartz, K. D. Niswender, *J. Clin. Endocrinol. Metab.* **89**, 5889 (2004).
22. Y. Zhang et al., *Nature* **372**, 425 (1994).
23. R. B. Harris et al., *Endocrinology* **139**, 8 (1998).
24. M. W. Schwartz et al., *Diabetes* **45**, 531 (1996).
25. C. T. Montague et al., *Nature* **387**, 903 (1997).
26. B. I. Joffe, V. R. Panz, F. J. Raal, *Lancet* **357**, 1379 (2001).
27. M. L. Reitman, E. Arioglu, O. Gavrilova, S. I. Taylor, *Trends Endocrinol. Metab.* **11**, 410 (2000).
28. K. Ebihara et al., *Diabetes* **50**, 1440 (2001).
29. E. A. Oral et al., *N. Engl. J. Med.* **346**, 570 (2002).
30. E. Asilmaz et al., *J. Clin. Invest.* **113**, 414 (2004).
31. J. Magre et al., *Nature Genet.* **28**, 365 (2001).
32. L. Van Maldergem et al., *J. Med. Genet.* **39**, 722 (2002).
33. M. W. Schwartz, S. C. Woods, D. Porte Jr., R. J. Seeley, D. G. Baskin, *Nature* **404**, 661 (2000).
34. J. T. Clark, P. S. Kalra, S. P. Kalra, *Endocrinology* **117**, 2435 (1985).
35. C. M. Kozl, J. E. Briggs, M. K. Grace, A. S. Levine, C. J. Billington, *Am. J. Physiol.* **275**, R471 (1998).
36. M. M. Ollmann et al., *Science* **278**, 135 (1997).
37. J. L. Marks, K. Waite, *J. Neuroendocrinol.* **9**, 99 (1997).
38. A. M. van den Hoek et al., *Diabetes* **53**, 2529 (2004).
39. J. R. Shutter, M. Graham, A. C. Kinsey, S. Scully, R. Luthy, K. L. Stark, *Genes Dev.* **11**, 593 (1997).
40. T. Adage et al., *J. Neurosci.* **21**, 3639 (2001).
41. M. A. Cowley et al., *Nature* **411**, 480 (2001).
42. M. W. Schwartz et al., *Diabetes* **46**, 2119 (1997).
43. R. D. Cone, *Trends Endocrinol. Metab.* **10**, 211 (1999).
44. D. G. Hardie, *Endocrinology* **144**, 5179 (2003).
45. Y. Minokoshi et al., *Nature* **428**, 569 (2004).
46. J. T. Deeney, M. Prentki, B. E. Corkey, *Semin. Cell Dev. Biol.* **11**, 267 (2000).
47. G. C. Yaney, B. E. Corkey, *Diabetologia* **46**, 1297 (2003).
48. T. M. Loftus et al., *Science* **288**, 2379 (2000).
49. Z. Hu, S. H. Cha, S. Chohan, M. D. Lane, *Proc. Natl. Acad. Sci. U.S.A.* **100**, 12624 (2003).
50. E. K. Kim et al., *J. Biol. Chem.* **279**, 19970 (2004).
51. K. A. Takahashi, J. L. Smart, H. Liu, R. D. Cone, *Endocrinology* **145**, 184 (2004).
52. S. Obici et al., *Diabetes* **51**, 271 (2002).
53. A. Pocai, S. Obici, G. Schwartz, L. Rossetti, *Cell Metab.*, in press.
54. D. Porte Jr., *Diabetes Metab. Res. Rev.* **17**, 181 (2001).
55. Supported by NIH grants DK52989, DK683840, and NS32273 and by the Diabetes Endocrinology Research Center and Clinical Nutrition Research Unit of the University of Washington.

10.1126/science.1104344