Insulin Resistance and Hyperinsulinemia

Is hyperinsulinemia the cart or the horse?

MICHAEL H. SHANIK, MD[1]
YUPING XU, MD[2]
JAN ŠKRHA, MD, DSC[3]
RACHEL DANKNER, MD, MPH[4]
YEHIEL ZICK, PHD[5]
JESSE ROTH, MD[2,6]

Insulin resistance, recently recognized as a strong predictor of disease in adults, has become the leading element of the metabolic syndrome and renewed as a focus of research. The condition exists when insulin levels are higher than expected relative to the level of glucose. Thus, insulin resistance is by definition tethered to hyperinsulinemia. The rising prevalence of medical conditions where insulin resistance is common has energized research into the causes. Many causes and consequences have been identified, but the direct contributions of insulin itself in causing or sustaining insulin resistance have received little sustained attention. We examine situations where insulin itself appears to be a proximate and important quantitative contributor to insulin resistance. *1*) Mice transfected with extra copies of the insulin gene produce basal and stimulated insulin levels that are two to four times elevated. The mice are of normal weight but show insulin resistance, hyperglycemia, and hypertriglyceridemia. 2) Somogyi described patients with unusually high doses of insulin and hyperglycemia. Episodes of hypoglycemia with release of glucose-raising hormones, postulated as the culprits in early studies, have largely been excluded by studies including continuous glucose monitoring. *3*) Rats and humans treated with escalating doses of insulin show both hyperinsulinemia and insulin resistance. *4*) The pulsatile administration of insulin (rather than continuous) results in reduced requirements for insulin. *5*) Many patients with insulinoma who have elevated basal levels of insulin have reduced (but not absent) responsiveness to administered insulin. In summary, hyperinsulinemia is often both a result and a driver of insulin resistance.

***Diabetes Care* 31 (Suppl. 2):S262–S268, 2008**

Insulin resistance has been assigned a central place in the metabolic disturbances associated with obesity and type 2 diabetes. Early studies (referred to later under historical notes, including the citation to work by Modan et al.) were crystallized and brought to fruition by Reaven (1), who proposed in 1988 that the cluster of insulin resistance (and by definition, hyperinsulinemia), impaired glucose tolerance, abnormalities of plasma lipids, and hypertension were part of a single syndrome, Syndrome X. It has also been called the insulin resistance syndrome, the deadly quartet, and more commonly, the metabolic syndrome.

More recently, Reaven et al. focused on insulin resistance as the key feature. In a prospective study of 208 people over 4–11 years, Facchini et al. (2) showed that insulin resistance was a powerful independent predictor of a wide range of serious illnesses, including stroke, type 2 diabetes, cardiovascular disease, hypertension, and even cancer. Subjects in the upper tertile of insulin resistance showed a very high prevalence of these illnesses, the lowest tertile had very few, and the middle tertile showed an intermediate prevalence (Fig. 1).

Insulin resistance is defined as a reduced responsiveness of a target cell or a whole organism to the insulin concentration to which it is exposed. It should be recognized that in vivo insulin resistance is tethered to hyperinsulinemia. In contrast to the prevailing view that assigns a dominant role to insulin resistance, we examine in this article the possible role of hyperinsulinemia, especially in the basal state, in sustaining, expanding, or initiating the insulin resistance. Particularly remarkable will be the severity of the insulin resistance (and the magnitude of insulin secretory defects) brought about by modest (twofold) elevations in basal insulin concentrations in mice with transgenic overexpression of insulin. Twofold elevations in basal insulin levels are common in patients with insulin resistance associated with obesity or type 2 diabetes. We review other examples where basal hyperinsulinemia initiates and significantly contributes to insulin resistance. Hopefully, this information will provide new insight into our understanding of obesity and type 2 diabetes.

HORMONE REGULATES TISSUE SENSITIVITY

— A hormone acutely stimulates its target cell and simultaneously resets the responsiveness of the target cell to subsequent doses of hormone. Homologous desensitization, the ability of a stimulatory ligand to desensitize its target cells to its action, is widespread. Let us examine two extreme examples where persistently high hormone levels totally desensitize the target cell to subsequent action by that hormone.

Patients with choriocarcinoma who have very high levels of human chorionic gonadotropin (hCG) may show no signs of excess gonadotropins (3) and are unresponsive to injected human chorionic gonadatropin (4). Extracts of the tumor do have biologically active hormone. After cure of the tumor, patients are responsive to injected human chorionic gonadatropin.

A more familiar example is with gonadotropin-releasing hormone (GnRH). Under normal circumstances, GnRH is secreted in a pulsatile fashion. When this

From the [1]Division of Endocrinology, North Shore–Long Island Jewish Health System, Lake Success, New York; the [2]Feinstein Institute for Medical Research, North Shore–Long Island Jewish Health System, Manhasset, New York; the [3]Department of Internal Medicine 3, 1st Faculty of Medicine, Charles University, Prague, Czech Republic; the [4]Cardiovascular Epidemiology Unit, Gertner Institute for Epidemiology and Health Policy Research, Tel-Hashomer, Israel; the [5]Department of Molecular Cell Biology, Weizmann Institute of Science, Rehovot, Israel; and the [6]Department of Internal Medicine, Albert Einstein College of Medicine, New York City, New York.

Address correspondence and reprint requests to Jesse Roth, MD, 149-37 Powells Cove Blvd., Whitestone NY 11357. E-mail: jesserothmd@hotmail.com.

The authors of this article have no relevant duality of interest to declare.

This article is based on a presentation at the 1st World Congress of Controversies in Diabetes, Obesity and Hypertension (CODHy). The Congress and the publication of this article were made possible by unrestricted educational grants from MSD, Roche, sanofi-aventis, Novo Nordisk, Medtronic, LifeScan, World Wide, Eli Lilly, Keryx, Abbott, Novartis, Pfizer, Generx Biotechnology, Schering, and Johnson & Johnson.

Abbreviations: GnRH, gonadotropin-releasing hormone; IRS, insulin receptor substrate.

DOI: 10.2337/dc08-s264

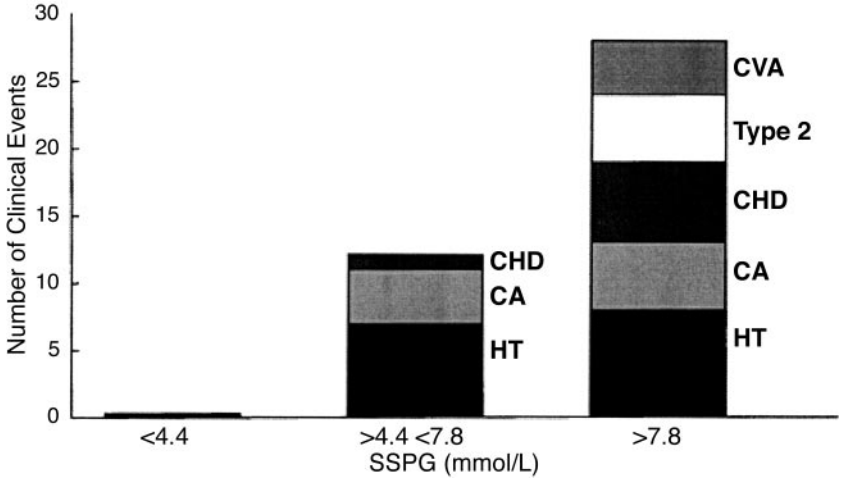

Figure 1—*The number of clinical events observed, as a function of insulin resistance tertile at baseline. CA, cancer; CHD, coronary heart disease; HT, hypertension; SSPG, steady-state plasma glucose (determined by continuous infusion of somatostatin, insulin, and glucose during a 75-g oral glucose tolerance test). Plasma glucose and insulin concentrations were drawn every 10 min during the last 30 min of the infusion. The average of the last four measurements was used to define the SSPG. There were 28 events in the highest tertile (SSPG >7.8 mmol/l), 12 in the intermediate tertile (SSPG > 4.4 < 7.8 mmol/l), and none in the most insulin-sensitive tertile (SSPG <4.4 mmol/l). From Facchini et al. (2)*

pattern of secretion is mimicked by exogenous injections, fertility can be induced in patients who have a disruption in GnRH release and/or function. When the hormone is given persistently, fertility and its other effects are blocked. Indeed, this feature of the hormone is used therapeutically in patients with idiopathic precocious puberty. With continuously elevated levels of GnRH, the precocious puberty is inhibited. Removal of the hormone is followed rapidly by a recrudescence of the pubescent process (5).

In both cases, the high hormone levels produce essentially complete unresponsiveness to the hormone. The insensitivity is reversed by removing the excess hormone. In the case of insulin resistance, responsiveness of target cells is considerably diminished but never completely lost. An acute rise in insulin is stimulatory, but persistently elevated levels of insulin desensitize the target cells through multiple mechanisms, including effects at the level of the insulin receptor (6) and at several sites beyond the receptor (7,8). A sustained elevated level of insulin, immaterial of its origin, typically leads to generalized insulin resistance. The ability of insulin to desensitize target cells to its own effects is best illustrated in a group of mice that have chronic overexpression of insulin.

TRANSGENIC HYPERINSULINEMIA

— Mice were stably transfected with 0, 8, or 32 extra copies of the human insulin gene (9). The transfected mice had elevated basal plasma insulin levels that were respectively two and four times higher than normal. They had normal weight and normal fasting glucose levels, but they displayed elevated postprandial glucose associated with an exaggerated insulin response to glucose (Fig. 2). The mice also showed diminution in hyperglycemia during an insulin tolerance test (Fig. 3). The hyperinsulinemia-induced insulin resistance was associated with reduced insulin receptor binding as well as significant hypertriglyceridemia that was correlated with the degree of hyperinsulinemia. We conclude that hyperinsulinemia in the basal state leads to generalized insulin resistance associated with disturbances in glucose metabolism and insulin secretion. That these mice were thin, did not develop antibodies to insulin, and had normal fasting glucose simplified the interpretation of the findings.

INSULIN RESISTANCE DISRUPTS INSULIN SECRETION

— Type 2 diabetes is often associated with basal hyperinsulinemia, reduced sensitivity to insulin, and disturbances in insulin release. In transgenic mice, basal hyperinsulinemia and reduction in target cell sensitivity to insulin were associated with a disturbance in insulin release from the β-cell. There was a delayed onset of insulin secretion in response to glucose, followed by a prolonged hyperinsulinemic phase. Are these disturbances due to insulin resistance at the level of the β-cell? Might we expect an insulin secretory defect in any condition associated with generalized hyperinsulinemia and insulin resistance? In this section, we will summarize data showing that insulin resistance limited to the pancreatic β-cell is capable of causing major disturbances in insulin secretion.

Genetic ablation of the insulin receptor only in the pancreatic β-cell of mice causes a defect in insulin secretion that is similar to that observed in type 2 diabetes (10). The mice show a loss in first-phase insulin secretion in response to glucose, but not to arginine, similar to that seen in humans with type 2 diabetes. The mice with β-cell–specific insulin receptor knockout (βIRKO) exhibit progressively impaired glucose tolerance over 6 months. The mechanism of this effect is complex, but the reduction in β-cell mass and islet number appear to be minor (Table 1) (11). The important role of the insulin response pathway in the function of the normal pancreatic β-cell is demonstrated by these studies. Insulin resistance at the level of the β-cell, coupled with peripheral insulin resistance, might provide a unifying hypothesis to explain the pathophysiology of type 2 diabetes in humans.

In a complementary study, deletion of the IGF-I receptor only in β-cells resulted in hyperinsulinemia (both fasted and fed) and glucose intolerance without a reduction in β-cell mass (12). Likewise, a mouse model lacking functional receptors for both insulin and IGF-I in β-cells only (βDKO) exhibited a normal level of islet cells up to 5 days, indicating that the insulin and IGF-1 pathways are not essential for islet cell development (13). However, this same mouse model exhibited a significant decline in the levels of islet cells at 2 weeks. Furthermore, 3 weeks after birth, they developed diabetes. Taken together, these data as well as data from other related knockout models suggest that insulin and IGF-1–dependent pathways are not critical for β-cell development, but reduced action of these hormones in the β-cells produces defects in insulin secretion and possibly even diabetes.

REVIEW OF PRIMARY HYPERINSULINEMIA IN VIVO

— Starting in 1938, Somogyi reported patients with poorly controlled

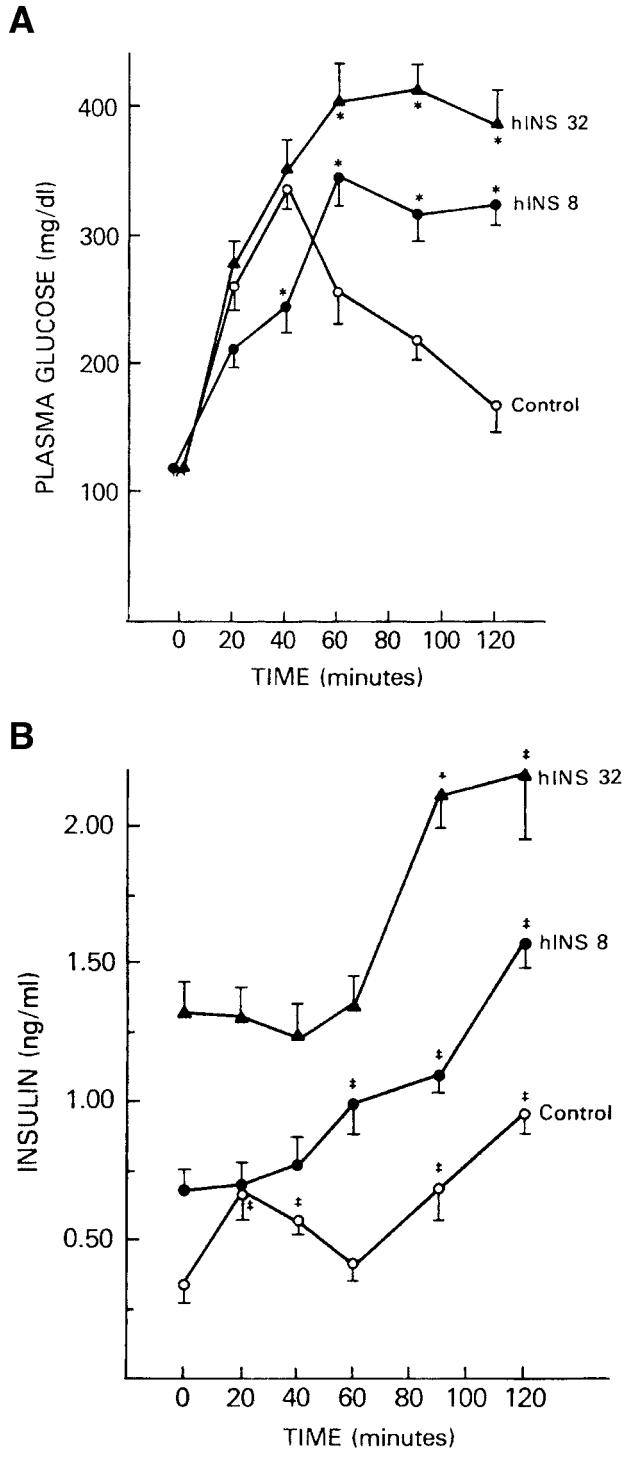

Figure 2—*Glucose tolerance tests in transgenic hyperinsulinemic (thin) mice. After an overnight fast, animals were injected intraperitoneally with glucose (2 mg/g body wt). Blood samples were taken at time points up to 120 min after injection for measurements of plasma glucose* (A) *and plasma insulin* (B)*. Points each represent the mean ± SE of nine or more individual measurements. Adapted from Marban and Roth (9).*

hyperglycemia who were receiving unexpectedly large doses of insulin in whom the hyperglycemia was ameliorated by reducing (rather than increasing) the insulin dose (14). He attributed this phenomenon to episodes of hypoglycemia (often undetected) that provoked release of counterregulatory hormones. Recent studies, including studies of such patients with sensitive methods that have excluded antecedent hypoglycemia as the cause, have shed doubt on his original explanation (15). We suggest that insulin-induced insulin resistance is the most likely mechanism.

Insulin resistance is associated with continuous exposure to high levels of insulin. Regardless of whether the insulin resistance or the basal hyperinsulinemia came first, the hyperinsulinemia itself might perpetuate the insulin resistance. Several in vivo studies, in which insulin was administered at high levels (similar to those found in insulin-resistant states), have confirmed that basal hyperinsulinemia can lead to insulin resistance. Increasing doses of NPH insulin in rats decreased the number of insulin receptors on target tissues with a corresponding decrease in cell sensitivity to insulin (16). By using a similar technique of administering gradually increasing doses of NPH insulin to rats, both downregulation of the insulin receptors and postreceptor defects were demonstrated (17). Rizza et al. (18) found that continuous (40-h) hyperinsulinemia in humans significantly reduced glucose utilization and overall glucose metabolism at submaximally and maximally effective plasma insulin concentrations. These studies indicate that hyperinsulinemia at levels similar to those observed in many insulin-resistant states can produce insulin resistance.

PULSATILE INSULIN MINIMIZES DESENSITIZATION

— Studies comparing continuous versus pulsatile administration of insulin have further supported the hypothesis that continuous hyperinsulinemia can cause insulin resistance. In healthy subjects, pulsatile delivery of insulin had a more robust hypoglycemic effect than continuous delivery (19–21). This phenomenon has also been shown in subjects with diabetes (21–23) as well as in an animal model of diabetes (24).

The efficacy of many hormones is greater when secreted in an oscillatory or pulsatile fashion. Luteinizing hormone, GnRH, growth hormone, and adrenocorticotropic hormone exhibit pulsatile patterns of release. The theoretical advantage of intermittent release is to minimize desensitization, thereby enhancing the action of the hormone. Similar to other hormones, insulin release is pulsatile, with rapid low-amplitude pulses every 8–15 min (25,26), as well as slower ultradian oscillations (27,28). Oscillatory pat-

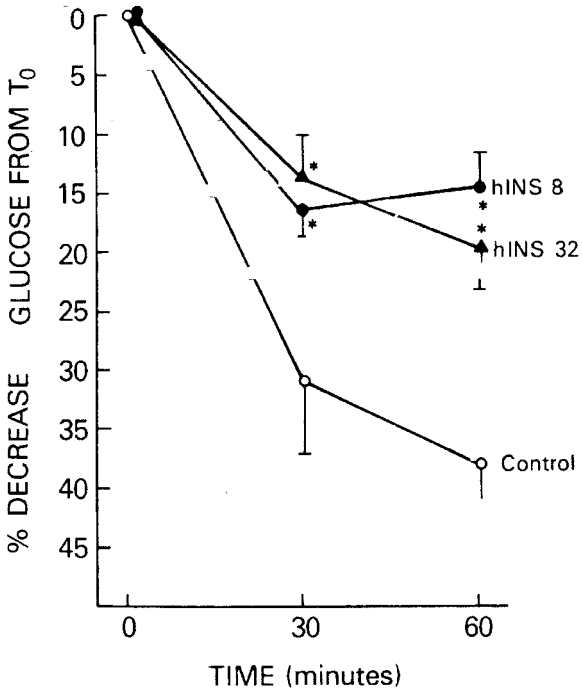

Figure 3— *Insulin tolerance tests in transgenic hyperinsulinemic (thin) mice. Mice were injected intraperitoneally with insulin (0.5 mU/g body wt). Blood for glucose determinations was drawn before and at 30 and 60 min after insulin injection. Each point represents the mean ± SE of 6–10 individual glucose determinations.* *P $<$ *0.02 vs. control. Adapted from Marban and Roth (9).*

terns are considered important in maintaining glucose within the normal range.

Enhanced action of insulin in the setting of pulsatile release has been supported by in vitro studies, in which hepatocytes were perfused with either a constant or pulsatile delivery of insulin. Insulin receptor expression was significantly higher in hepatocytes exposed to oscillatory concentrations of insulin compared with continuous insulin exposure (29). Furthermore, isolated rat adipocytes exposed to continuous hyperinsulinemia led to a dose-dependant loss of insulin receptors, as well as a marked postreceptor defect in glucose transport (30). In insulin-resistant states, continuous exposure to insulin without pulsatility might be capable of producing insulin resistance.

BASAL HYPERINSULINEMIA WITH INSULINOMAS

— Patients with insulinoma provide an alternative setting to study the effects of persistent basal hyperinsulinemia on insulin sensitivity. Like patients with insulin resistance due to other conditions, insulinoma patients have the following: *1*) elevated levels of circulating insulin, *2*) insulin resistance, *3*) impaired insulin secretion in response to glucose (31,32), *4*) an increase in the long isoform (lower insulin binding affinity) of the insulin receptor (33), *5*) reduced insulin effects at receptor and postreceptor sites (34,35), and *6*) reduced sensitivity to insulin during clamp studies (36). Surgical resection of the insulinoma completely restored glucose metabolism and insulin sensitivity after normalization of insulin secretion from β-cells (36,37).

While insulinoma patients differ in some ways from other patients with hyperinsulinemia and insulin resistance (e.g., immunologic assays of insulin may overestimate the bioactivity of circulating insulin of insulinoma patients; the basal secretion from the tumor may suppress the normal pancreas), the primary hyperinsulinemia remains a dominant feature.

MECHANISMS OF INSULIN-INDUCED RESISTANCE TO INSULIN

— Like other hormone-sensitive pathways, the intracellular pathway of insulin action is continuously being regulated by a multiplicity of influences. In this section, we focus on the effects of insulin itself on the sensitivity of its own pathway with particular emphasis on homologous desensitization, i.e., the dampening effects produced by continuous exposure of the target cells to stimulatory levels of insulin.

The insulin receptor itself is a well-studied mediator of negative feedback that involves reduction in receptor affinity, reduction in the number of receptors exposed on the surface of the target cell, and diminution of the effectiveness of the receptor as a transmitter of stimulatory signals. Each insulin receptor has two binding sites for insulin. One insulin molecule binds with high affinity, whereas binding of a second insulin molecule occurs with lower affinity (38). At increasing concentrations of insulin, occupancy of receptor sites increases, but average affinity diminishes ("negative cooperativity") (39).

Another mechanism for insulin-induced regulation of receptor affinity is

Table 1—*Insulin secretory defects in knockout models*

	Pancreatic insulin content (μg/mg pancreas) (2-week-old mice)	β-Cell mass (mg) (2-week-old mice)	Fasting insulin level (ng/ml)	Fed insulin level (ng/ml)	Insulin secretion (ng(ng DNA)$^{-1}$ (60 min)$^{-1}$) (4-week-old mice)	Fasting blood glucose (mg/dl)
Control	0.32 ± 0.06	1.2 ± 0.1	0.4 ± 0.1	1.9 ± 0.4	1.4 ± 0.3	72 ± 13
βIRKO	0.27 ± 0.05	1.0 ± 0.2	0.9 ± 0.08*	2.6 ± 1.1	1.3 ± 0.2	58 ± 9
βIGF1RKO	0.35 ± 0.06	0.9 ± 0.4	0.9 ± 0.2*	2.4 ± 0.9	1.3 ± 0.2	82 ± 9
βDKO	0.11 ± 0.05*	0.5 ± 0.1*	Not available	0.6 ± 0.6*	0.2 ± 0.5*	396 ± 102*

Data are compiled from References 10–13. *$P < 0.05$ vs. control mice. βIRKO, β-cell–specific insulin receptor knockout; βIGF1RKO, β-cell–specific IGF-1 receptor knockout; βDKO, β-cell–specific insulin and IGF-1 receptor knockout.

exercised via regulation of the relative proportion of the two molecular isoforms (40) of the insulin receptor. Continuous exposure to insulin results in a reduction in the proportion of short (higher affinity) isoforms to long (lower affinity) isoforms. The relative contribution from changes in production versus degradation rates has not been fully established.

Continuous exposure to insulin causes a reduction in the number of receptors exposed on the cell surface by promoting internalization as well as degradation of hormone-occupied receptors (6). The insulin receptor is a tyrosine kinase that activates itself and then transmits its stimulatory message by promoting the phosphorylation of selected tyrosines on the receptor and on postreceptor partner molecules such as insulin receptor substrate family members IRS-1 and IRS-2 in the family of insulin receptor substrates. With continuous exposure to insulin, the receptor's kinase activity is diminished, probably because of combined effects of phosphorylation of serine residues on the receptor, dephosphorylation of tyrosines by the action of phosphatases, and the binding of inhibitory molecules (41–45).

Receptor-mediated tyrosine phosphorylation activates downstream proteins, especially the IRS proteins (mentioned earlier) to promote the downstream activation of the target cell. The IRS proteins also become phosphorylated on serine (and threonine) residues, probably by the action of multiple kinases. Serine phosphorylated forms of the IRS proteins have reduced ability to activate downstream elements and also act upstream to inhibit the activity of the insulin receptor.

Several other molecules downstream in the insulin pathway (e.g., *m*-TOR and phosphatidylinositol 3-kinase) transmit the activation process downstream and also provide upstream negative feedback signals. In addition, chronic exposure of the cell to insulin may result in a diminished concentration of downstream elements, including key components such as the IRS proteins (44,45).

The insulin-stimulated pathway, as noted at the beginning of this section, is regulated by heterologous agents. Interestingly, some of these heterologous modifiers (e.g., tumor necrosis factor and free fatty acids) are themselves under the influence of insulin (46,47).

This brief superficial survey shows that insulin regulates its own sensitivity. The mechanisms occur in a concentration- and time-dependent way. They are complex and as yet incompletely defined. The pathways vary between target cells, between pathways within an individual target cell, and among pathological states and individual patients. While the complexity is daunting, it provides opportunities for specific therapeutic interventions.

HISTORICAL NOTES — Insulin resistance was initially recognized in insulin-treated patients who required larger than usual doses of insulin. Infections, endocrinopathies, allergy to insulin, and (later) antibodies to insulin were recognized as early causes (48–51).

The recognition of insulin resistance in patients who were not receiving insulin awaited the introduction of *1*) the insulin tolerance test, *2*) measurement of the effects of insulin infused into arterial blood of the forearm (52,53), *3*) the immunoassay of insulin (the first reliable quantitative measure of endogenous circulating insulin) (54), and *4*) clamp techniques.

Our discussion here is devoted to moderate insulin resistance, i.e., a few-fold diminution in sensitivity to insulin (extreme insulin resistance, e.g., a 5- to 10-fold or more reduction in sensitivity to insulin was first described in patients with lipoatrophic diabetes and later in patients with high concentrations of anti-insulin antibodies after treatment with insulin). Later, patients with autoantibodies against the insulin receptor and patients with inborn defects of the insulin receptor were added to the list.

In the period just before widespread acceptance of the immunoassay, bioassays were in ascendancy, which detected plasma components that diminished insulin action in these assays; these substances were collectively labeled circulating insulin antagonists (55–57). The immunoassay swept away all but the circulating anti-insulin antibodies and well-defined hormones such as catecholamines, glucocorticoids, growth hormone, and glucagon. The immunoassay also left behind a negative attitude toward other circulating antagonists or inhibitors of insulin action. In our opinion, PC-1 and other well-defined circulating molecules deserve greater attention than they have been receiving. In retrospect, it is highly likely that the circulating antagonist of insulin action that everyone was searching for may be insulin itself. The introduction of direct studies of the insulin receptor (and later of postreceptor pathways) made those insights possible.

Whereas insulin resistance in general was linked to metabolism of glucose and later to other substrates in patients with obesity and type 2 diabetes, the link between hyperinsulinemia and other conditions arrived later. In 1981, hyperinsulinemia had been ascribed a pathogenetic role in obese hypertension via increased renal sodium retention (58). In 1985, Modan et al. (59) proposed that hyperinsulinemia, reflecting peripheral insulin resistance, is linked to hypertension, obesity, and glucose intolerance in humans, and in 1988, Modan et al. (60) further reported that hyperinsulinemia is characterized by jointly disturbed plasma lipids. The same year, Reaven (1) proposed the term "Syndrome X" for the cluster of insulin resistance and hyperinsulinemia, impaired glucose tolerance, abnormalities of plasma lipids, and hypertension, now commonly called the metabolic syndrome.

CONCLUSIONS/FUTURE PROSPECTS — Hyperinsulinemia in the basal state of any origin produces widespread insulin resistance. All tissues that have insulin receptor pathways will be affected, including the pancreatic β-cell, and possibly the brain (61,62). Defective insulin signaling at the β-cell impairs glucose-stimulated insulin release. At steady state, basal hyperinsulinemia generates and sustains insulin resistance, irrespective of where the pathology started. Hyperinsulinemia, insulin resistance, and impairment of glucose-stimulated insulin release are intertwined biologically. A single process (hyperinsulinemia) could generate all three simultaneously.

There are several factors that contribute to insulin release. In the basal state, free fatty acid levels act in part to stimulate the release of insulin. Obese subjects have high levels of free fatty acids, and this might be a major contributor to the hyperinsulinemia present in these patients (63). Basal insulin levels are such an important determinant of insulin sensitivity, it is important to understand the multiple elements that are driving the hyperinsulinemia in the basal state. It may be that the stimulus for basal hyperinsulinemia varies by patient and/or disease state.

One of the characteristics of hyperinsulinemic states, specifically the metabolic syndrome, is an elevated level of inflammatory markers, including cyto-

kines and C-reactive protein (64). Many cells of the innate immune system are sensitive to insulin and reduce their output of cytokines at insulin concentrations that are commonly encountered in vivo (46,47). It could be that the inflammatory background associated with obesity may be due to insulin resistance at the level of the inflammatory cells.

Basal hyperinsulinemia perpetuates insulin resistance by a wide range of mechanisms. Free fatty acids and other stimulators of insulin secretion have been defined, and these factors might be the initial insults that drive the excess insulin secretion. Understanding the pathophysiology of the basal hyperinsulinemia may provide guidance in the development of effective and specific therapies.

NOTES ADDED IN PROOF — A widely recommended approach to the control of hyperglycemia, which we endorse, is to add a parenteral insulin preparation that provides a constant background addition to circulating insulin for 12–24 h to augment or replace in vivo basal insulin secretion. We accept that empirically this practice improves control of glycemia. We hypothesize that were it possible to administer basal insulin as intermittent brief boluses, control of glycemia would be equal (or better), achieved with smaller doses of insulin and less insulin resistance systemically.

Parathyroid hormone provides another striking example of how homologous hormone regulates target cell sensitivity. Continuous hormone (e.g. with hyperparathyroidism) melts bones, while intermittent administration builds bones dramatically.

Hypothalamic obesity appears to be another example of insulin resistance where hyperinsulinemia may be driving insulin resistance (65).

References

1. Reaven GM: Banting lecture: role of insulin resistance in human disease. *Diabetes* 37:1595–1607, 1988
2. Facchini FS, Hua N, Abbasi F, Reaven GM: Insulin resistance as a predictor of age-related diseases. *J Clin Endocrinol Metab* 86:3574–3578, 2001
3. Berkowitz RS, Goldstein DP: Medical progress: chorionic tumors. *N Engl J Med* 335:1740–1748, 1996
4. Conti M, Harwood JP, Hsueh AJW, Dufau ML, Catt KJ: Gonadotropin-induced loss of hormone receptors and desensitization of adenylate cyclase in the ovary. *J Biol Chem* 251:7729–7731, 1976
5. Manasco PK, Peskovitz OH, Hill SC, Jones JM, Barnes KM, Hench KD, Loriaux DL, Cutler GB Jr: Six-year results of luteinizing hormone releasing hormone (LHRH) agonist treatment in children with LHRH-dependent precocious puberty. *J Pediatr* 115:105–108, 1989
6. Gavin JR III, Roth J, Neville DM Jr, De Meyts P, Buell DN: Insulin-dependent regulation of insulin receptor concentrations: a direct demonstration in cell culture. *Proc Natl Acad Sci U S A* 71:84–88, 1974
7. Le Marchand Y, Loten EG, Assimacopoulos-Jeannet F, Forgue ME, Freychet P, Jeanrenaud B: Effect of fasting and streptozotocin in the obese-hyperglycemic (*ob/ob*) mouse: apparent lack of a direct relationship between insulin binding and insulin effects. *Diabetes* 26:582–590, 1977
8. Zick Y: Role of Ser/Thr kinases in the uncoupling of insulin signaling. *Int J Obes* 27 (Suppl. 3):S56–S60, 2003
9. Marban SL, Roth J: Transgenic hyperinsulinemia: a mouse model of insulin resistance and glucose intolerance without obesity. In *Lessons from Animal Diabetes VI*. 6th ed. Shafrir E, Boston, Birkhauser, 1996, p. 201–224
10. Kulkarni RN, Brüning JC, Winnay JN, Postic C, Magnuson MA, Kahn CR: Tissue-specific knockout of the insulin receptor in pancreatic β cells creates an insulin secretory defect similar to that in type 2 diabetes. *Cell* 96:329–339, 1999
11. Otani K, Kulkarni RN, Baldwin AC, Krutzfeldt J, Ueki K, Stoffel M, Kahn CR, Polonsky KS: Reduced β-cell mass and altered glucose sensing impair insulin-secretory function in βIRKO mice. *Am J Physiol Endocrinol Metab* 286:E41–E49, 2004
12. Kulkarni RN, Holzenberger M, Shih DQ, Ozcan U, Stoffel M, Magnuson MA, Kahn CR: β-Cell-specific deletion of the Igf1 receptor leads to hyperinsulinemia and glucose intolerance but does not alter β-cell mass. *Nat Genet* 31:111–115, 2002
13. Ueki K, Okada T, Hu J, Liew CW, Assmann A, Dahlgren GM, Peters J, Shackman JG, Zhang M, Artner I, Satin LS, Stein R, Holzenberger M, Kennedy RT, Kahn CR, Kulkarni RN: Total insulin and IGF-1 resistance in pancreatic β cells causes overt diabetes. *Nat Genet* 38:583–588, 2006
14. Somogyi M, Kirstein M: Insulin as a cause of extreme hyperglycemia and instability. *Week Bull St Louis M Soc* 32:498, 1938
15. Hoi-Hansen T, Pedersen-Bjergaard U, Thorsteinsson B: The Somogyi phenomenon revisited using continuous glucose monitoring in daily life. *Diabetologia* 48: 2437–2438, 2005
16. Kobayashi M, Olefsky JM: Effect of experimental hyperinsulinemia on insulin binding and glucose transport in isolated rat adipocytes. *Am J Physiol Gastrointest Liver Physiol* 235:E53–E62, 1978
17. Martin C, Desai KS, Steiner G: Receptor and postreceptor insulin resistance induced by *in vivo* hyperinsulinemia. *Can J Physiol Pharmacol* 61:802–807, 1983
18. Rizza RA, Mandarino LJ, Genest J, Baker BA, Gerich JE: Production of insulin resistance by hyperinsulinemia in man. *Diabetologia* 28:70–75, 1985
19. Matthews DR, Naylor BA, Jones RG, Ward GM, Turner RC: Pulsatile insulin has greater hypoglycemic effect than continuous delivery. *Diabetes* 32:617–621, 1983
20. Schmitz O, Arnfred J, Nielsen OH, Beck-Nielsen H, Orskov H: Glucose uptake and pulsatile insulin infusion: euglycaemic clamp and [3-^{3}H] glucose studies in healthy subjects. *Acta Endocrinol (Copenh)* 113:559–563, 1986
21. Paolisso G, Sgambato S, Torella R, Varricchio M, Scheen A, D'Onofrio F, Lefebvre PJ: Pulsatile insulin delivery is more efficient than continuous infusion in modulating islet cell function in normal subjects and patients with type 1 diabetes. *J Clin Endocrinol Metab* 66:1220–1226, 1988
22. Paolisso G, Sgambato S, Passariello N, Scheen A, D'Onofrio F, Lefebvre PJ: Greater efficacy of pulsatile insulin in type 1 diabetics critically depends on plasma glucagon levels. *Diabetes* 35:566–570, 1987
23. Bratusch-Marrain PR, Komjati M, Waldhausl WK: Efficacy of pulsatile versus continuous insulin administration on hepatic glucose production and glucose utilization in type 1 diabetic humans. *Diabetes* 35:922–926, 1986
24. Koopmans SJ, Sips HCM, Krans HMJ, Radder JK: Pulsatile intravenous insulin replacement in streptozotocin diabetic rats is more efficient than continuous delivery: effects on glycaemic control, insulin-mediated glucose metabolism and lipolysis. *Diabetologia* 39:391–400, 1996
25. Lang DA, Matthews DR, Peto J, Turner RC: Cyclic oscillations of basal plasma glucose and insulin concentrations in human beings. *N Engl J Med* 301:1023–1027, 1979
26. Hansen BC, Jen KC, Pek SB, Wolfe RA: Rapid oscillations in plasma insulin, glucagon, and glucose in obese and normal weight humans. *J Clin Endocrinol Metab* 54:785–792, 1982
27. Simon C, Follenius M, Brandenberger G: Postprandial oscillations of plasma glucose, insulin and C-peptide in man. *Diabetologia* 30:769–773, 1987
28. Polonsky KS, Given BD, Van Cauter E: Twenty-four-hour profiles and pulsatile patterns of insulin secretion in normal and obese subjects. *J Clin Invest* 81:442–448, 1988
29. Goodner CJ, Sweet IR, Harrison HC: Rapid reduction and return of surface in-

sulin receptors after exposure to brief pulses of insulin in perfused rat hepatocytes. *Diabetes* 37:1316–1323, 1988
30. Marshall S, Olefsky JM: Effects of insulin incubation on insulin binding, glucose transport, and insulin degradation by isolated rat adipocytes. *J Clin Invest* 66:763–772, 1980
31. Nankervis A, Proietto J, Aitken P, Alford F: Hyperinsulinaemia and insulin insensitivity: studies in subjects with insulinoma. *Diabetologia* 28:427–431, 1985
32. Del Prato S, Riccio A, de Kreutzenberg SV, Dorella M, Avogaro A, Marescotti MC, Tiengo A: Mechanism of fasting hypoglycemia and concomitant insulin resistance in insulinoma patients. *Metabolism* 42: 24–29, 1993
33. Sbraccia P, D'Adamo M, Leonetti F, Caiola S, Iozzo P, Giaccari A, Buongiorno A, Tamburrano G: Chronic primary hyperinsulinaemia is associated with altered insulin receptor mRNA splicing in muscle of patients with insulinoma. *Diabetologia* 39:220–225, 1996
34. Bar R, Gorden P, Roth J, Siebert CW: Insulin receptors in patients with insulinomas: changes in receptor affinity and concentration. *J Clin Endocrinol Metab* 44: 1210–1213, 1977
35. Škrha J, Šindelka G, Haas T, Hilgertová J, Justová V: Comparison of insulin sensitivity in patients with insulinoma and obese type 2 diabetes mellitus. *Horm Metab Res* 28:595–598, 1996
36. Škrha J, Hilgertová J, Justová V: Insulin action in patients with insulinoma influenced by pharmacological and surgical therapy. *Exp Clin Endocrinol* 101:360–364, 1993
37. Pontiroli AE, Alberetto M, Capra F, Pozza G: The glucose clamp technique for the study of patients with hypoglycemia: insulin resistance as a feature of insulinoma. *J Endocrinol Invest* 13:241–245, 1990
38. De Meyts P, Bianco AR, Roth J: Site-site interactions among insulin receptors: characterization of the negative cooperativity. *J Biol Chem* 251:1877–1888, 1976
39. De Meyts P, Roth J, Neville DM Jr, Gavin JR 3rd, Lesniak MA: Insulin interactions with its receptors: experimental evidence for negative cooperativity. *Biochem Biophys Res Commun* 55:154–161, 1973
40. Seino S, Bell GI: Alternative splicing of human insulin receptor messenger RNA. *Biochem Biophys Res Commun* 159:312–316, 1989
41. Zick Y, Grunberger G, Podskalny JM, Moncada V, Taylor SI, Gorden P, Roth J: Insulin stimulates phosphorylation of serine residues in soluble insulin receptors. *Biochem Biophys Res Commun* 116:1129–1135, 1983
42. Kusari J, Kenner KA, Suh KI, Hill DE, Henry RR: Skeletal muscle protein tyrosine phosphatase activity and tyrosine phosphatase 1B protein content are associated with insulin action and resistance. *J Clin Invest* 93:1156–1162, 1994
43. Krebs DL, Hilton DJ: A new role for SOCS in insulin action: suppressor of cytokine signaling. *Sci STKE* PE6, 2003
44. Zick Y: Insulin resistance: a phosphorylation-based uncoupling of insulin signaling. *Trends Cell Biol* 11:437–441, 2001
45. Paz K, Hemi R, LeRoith D, Karasik A, Elhanany E, Kanety H, Zick Y: A molecular basis for insulin resistance: elevated serine/threonine phosphorylation of IRS-1 and IRS-2 inhibits their binding to the juxtamembrane region of the insulin receptor and impairs their ability to undergo insulin-induced tyrosine phosphorylation. *J Biol Chem* 272:29911–29918, 1997
46. Dandona P, Aljada A, Bandyopadhyay A: Inflammation: the link between insulin resistance, obesity and diabetes. *Trends Immunol* 25:4–7, 2004
47. Roth J, Qiang X, Marban SL, Redel H, Lowell BC: The obesity pandemic: Where have we been and where are we going? *Obes Res* 12:88S–101S, 2004
48. Sherrill JW, Lawrence R Jr: Insulin resistance: the mechanisms involved and the influence of infection and refrigeration. *U S Armed Forces Med J* 1:1399–1409, 1950
49. Lowell FC: Immunologic studies in insulin resistance. I. Report of a case exhibiting variations in resistance and allergy to insulin. *J Clin Invest* 23:225–231, 1944
50. Sherman WB: A case of coexisting insulin allergy and insulin resistance. *J Allergy* 21: 49–54, 1950
51. Paniagua ME: Insulin resistance; a review of the subject and presentation of two cases. *Bol Asoc Med PR* 42:17–29, 1950
52. Rabinowitz D, Zierler KL: Forearm metabolism in obesity and its response to intra-arterial insulin: characterization of insulin resistance and evidence for adaptive hyperinsulinism. *J Clin Invest* 41:2173–2181, 1962
53. Zierler KL, Rabinowitz D: Roles of insulin and growth hormone, based on studies of forearm metabolism in man. *Medicine* 42: 385, 1963
54. Yalow RS, Berson SA: Immunoassay of endogenous plasma insulin in man. *J Clin Invest* 39:1157–1175, 1960
55. Baird CW, Bornstein J: Plasma insulin and insulin resistance. *Lancet* 1:1111–1113, 1957
56. Vargas L, Taylor KW, Randle PJ: Insulin and an inhibitor of glucose uptake in protein fraction of normal human plasma. *Biochem J* 77:43–47, 1960
57. Vallance-Owen J: Insulin antagonists. *Br Med Bull* 16:214–218, 1960
58. DeFronzo RA: The effect of insulin on renal sodium metabolism: a review with clinical implications. *Diabetologia* 21:165–171, 1981
59. Modan M, Halkin H, Almog S, Lusky A, Eshkol A, Shefi M, Shitrit A, Fuchs Z: Hyperinsulinemia: a link between hypertension, obesity and glucose intolerance. *J Clin Invest* 75:809–817, 1985
60. Modan M, Halkin H, Lusky A, Segal P, Fuchs Z, Chetrit A: Hyperinsulinemia is characterized by jointly disturbed plasma VLDL, LDL, and HDL levels: a population-based study. *Arteriosclerosis* 8:227–236, 1988
61. Plum L, Belgardt BF, Brüning JC: Central insulin action in energy and glucose homeostasis. *J Clin Invest* 116:1761–1766, 2006
62. Porte D, Baskin DG, Schwartz MW: Insulin signaling in the central nervous system: a critical role in metabolic homeostasis and disease from C. elegans to humans. *Diabetes* 54:1264–1276, 2005
63. Boden G, Chen X, Iqbal N: Acute lowering of plasma fatty acids lowers basal insulin secretion in diabetic and nondiabetic subjects. *Diabetes* 47:1609–1612, 1998
64. Rutter MK, Meigs JB, Sullivan LM, D'Agostino RB, Wilson PWF: C-reactive protein, the metabolic syndrome, and prediction of cardiovascular events in the Framingham offspring study. *Circulation* 110:380–385, 2004
65. Lustig RH, Hinds PS, Ringwald-Smith K, Christensen RK, Kaste SC, Schreiber RE, Rai SN, Lensing SY, Wu S, Xiong X: Octreotide therapy of pediatric hypothalamic obesity: a double-blind, placebo-controlled trial. *J Clin Endocrinol Metab* 88: 2586–2592, 2003