

# Selective versus Total Insulin Resistance: A Pathogenic Paradox

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Mice with type 2 diabetes manifest selective hepatic insulin resistance: insulin fails to suppress gluconeogenesis but continues to activate lipogenesis, producing the deadly combination of hyperglycemia and hypertriglyceridemia. In this issue of *Cell Metabolism*, [Biddinger et al. \(2008\)](#) show that mice with total hepatic insulin resistance exhibit hyperglycemia without hypertriglyceridemia—a state paradoxically less severe than selective insulin resistance.

Humans with type 2 diabetes mellitus exhibit the classic triad of hyperinsulinemia, hyperglycemia, and hypertriglyceridemia. Hyperglycemia in the face of hyperinsulinemia is attributed to insulin resistance. In diabetic subjects, the major insulin-resistant organs are liver, muscle, and adipose tissue. The precise contribution that each organ makes to hyperglycemia and hypertriglyceridemia is not known. To answer this question, Kahn and associates have conducted systematic studies in mice in which they have ablated the insulin receptor gene in each of these suspect organs ([Biddinger and Kahn, 2006](#)). The latest installment is found in this issue, where [Biddinger et al. \(2008\)](#) examine glucose and lipid metabolism in liver-specific insulin receptor knockout (LIRKO) mice ([Michael et al., 2000](#)). [Biddinger et al.](#) describe several disturbances of metabolism in the LIRKO mice. Here, we focus on the central issue of the insulin resistance triad.

In their initial description of LIRKO mice, [Michael et al. \(2000\)](#) reported that selective elimination of the insulin receptor in livers of young mice produced both fasting hyperglycemia and hyperinsulinemia. Despite extremely high levels of circulating insulin, the mice exhibited marked hyperglycemia in response to an exogenous glucose load and a diminished response to injected insulin, consistent with systemic insulin resistance.

[Biddinger et al. \(2008\)](#) explore the consequences of hepatic insulin receptor deficiency for the third element of the insulin resistance triad, namely hypertriglyceridemia. Herein lies the paradox. In LIRKO mice, the correlation with type 2 diabetes breaks down. Despite hyperglycemia and

hyperinsulinemia, LIRKO mice manifest low plasma triglycerides and no elevation of hepatic triglycerides.

The explanation for the paradox is found in the dual actions of insulin in the liver, as illustrated in [Figure 1](#). As shown in [Figure 1A](#), under normal conditions, dietary glucose stimulates insulin secretion from the pancreas. The insulin travels directly to the liver via the portal vein, where it elicits two key actions at the level of gene transcription. First, insulin stimulates the phosphorylation of FoxO1, a transcription factor that activates gluconeogenesis ([Matsumoto et al., 2006](#)). Insulin-stimulated phosphorylation prevents FoxO1 from entering the nucleus, and hence it downregulates genes required for gluconeogenesis, most prominently phosphoenolpyruvate carboxykinase (PEPCK) and glucose 6-phosphatase (G6Pase). The result is a decrease in hepatic glucose output, which helps to keep blood glucose low.

The second action of insulin is to activate the transcription factor SREBP-1c, which enhances transcription of genes required for fatty acid and triglyceride biosynthesis, most prominently acetyl-coenzyme A carboxylase (ACC) and fatty acid synthase (FAS) ([Brown and Goldstein, 1997](#); [Horton et al., 2002](#)). Insulin activates SREBP-1c by two mechanisms: (1) it increases transcription of the *SREBP-1c* gene, and (2) it increases the amount of nuclear SREBP-1c, most likely by increasing the conversion of the membrane-bound precursor to its cleaved nuclear form ([Shimomura et al., 2000](#); [Ferre and Foufelle, 2007](#)). The newly produced triglycerides are secreted in very low-density lipoprotein (VLDL), which delivers triglycerides to fat for storage and to

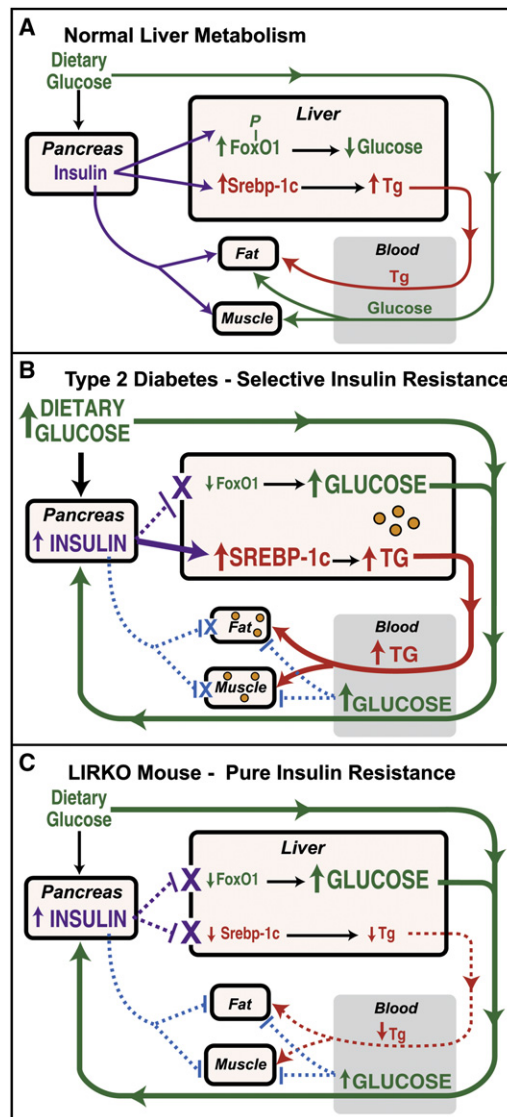
muscle for combustion. Uptake of VLDL-derived fatty acids in adipose tissue is facilitated by insulin, which increases the amount of lipoprotein lipase on the surface of endothelial cells.

[Figure 1B](#) shows how this regulatory system goes awry in two mouse models of insulin-resistant type 2 diabetes, *ob/ob* mice and lipodystrophic mice, both of which have increased food intake secondary to a deficiency of the appetite-suppressant hormone leptin. Increased food intake increases insulin secretion. In the liver, the FoxO1 pathway becomes insulin resistant. Despite extremely high insulin levels, the mRNAs for PEPCK and G6Pase remain high, and gluconeogenesis continues. Despite insulin resistance in the FoxO1 pathway, insulin sensitivity is maintained in the SREBP-1c pathway ([Shimomura et al., 2000](#)). Thus, nuclear SREBP-1c levels are extremely high, fatty acid synthesis is accelerated, and triglycerides accumulate in the liver. Excess triglycerides are secreted in VLDL, raising plasma triglyceride levels. Fatty acids derived from these triglycerides worsen the insulin-resistant state in muscle and adipose tissue. The net result is the classic type 2 diabetic triad—hyperglycemia, hyperinsulinemia, and hypertriglyceridemia.

[Figure 1C](#) shows how glucose and fatty acid metabolism in LIRKO mice differs from that in mouse models of type 2 diabetes. In LIRKO mice, food intake is normal, but hepatic insulin resistance is total. Insulin cannot suppress gluconeogenesis, and thus the liver continues to secrete glucose. Insulin also cannot activate SREBP-1c, and so hepatic triglycerides and circulating VLDL are low. The net result is hyperinsulinemia and hyperglycemia without

hypertriglyceridemia. In their initial paper, Michael et al. (2000) supplied evidence that the hyperinsulinemia in LIRKO mice results in part from a failure of the receptor-deficient liver to clear insulin from the circulation via receptor-mediated endocytosis. In the fasted state, the high systemic insulin levels do not produce hypoglycemia, indicating that fat and muscle are insulin resistant in LIRKO mice despite the lack of hypertriglyceridemia. These observations are consistent with the idea that hyperinsulinemia itself elicits insulin resistance in peripheral tissues, as postulated 15 years ago (McGarry, 1992).

The concept of selective insulin resistance in the liver assumes increased importance with the realization that elevated fatty acids and triglycerides make detrimental contributions to the diabetic state. The foundation for this concept was laid in 1992 with a prescient opinion piece written by the late Denis McGarry entitled "What if Minkowski Had Been Ageusic? An Alternative Angle on Diabetes" (McGarry, 1992). McGarry pointed out the toxic role played by elevated VLDL triglycerides in patients with type 2 diabetes. In particular, he marshaled data showing that some of these triglycerides deposit in muscle, where they enhance insulin resistance. Triglycerides also accumulate in the liver, where they can produce nonalcoholic steatohepatitis (NASH), an increasingly frequent cause of cirrhosis and liver failure. Some of the excess triglycerides also deposit in  $\beta$  cells of the pancreas, where they contribute to the eventual  $\beta$  cell failure that leads to frank diabetes (Unger, 1995). Lipotoxicity is a term that has been coined to designate the detrimental effects of triglyceride accumulation in various organs (Lee et al., 1994; Unger, 1995). Whether the toxic moieties are fatty acids, triglycerides, or other compounds derived from fatty acids is not settled. In this regard, it is of interest that hyperglycemia declines in LIRKO mice with age (Michael et al., 2000), a finding opposite that observed in *ob/ob* and lipodystrophic mice. The lack of diabetes progression in LIRKO mice might be attributable, at least in part, to a lack of lipotoxicity.



**Figure 1. Model Illustrating the Paradox by which Selective Insulin Resistance in the Liver Produces a More Severe Metabolic Defect than Total Insulin Resistance**

(A) Normal response of the liver to a glucose load. Insulin leads to decreased gluconeogenesis and increased synthesis of fatty acids and triglycerides (Tg).

(B) Selective insulin resistance in liver of mice with type 2 diabetes. Insulin fails to decrease gluconeogenesis, but it continues to stimulate synthesis of fatty acids and Tg. This produces the deadly combination of hyperglycemia and hypertriglyceridemia.

(C) Total insulin resistance in liver of LIRKO mice. Insulin fails to decrease gluconeogenesis, and it also fails to stimulate synthesis of fatty acids and Tg. This leads to hyperglycemia without hypertriglyceridemia, a state that may have consequences less severe than those observed with the combined elevation.

From a scientific standpoint, the paradox of selective insulin resistance raises the question of the regulatory step in which the gluconeogenic and lipogenic pathways diverge. The effect of insulin on both path-

ways requires the insulin receptor. However, at some distal point, the FoxO1 pathway becomes insensitive to insulin, whereas the SREBP-1c pathway remains sensitive. Identification of this branch point is a central question for future research.

In type 2 diabetes, selective insulin resistance has implications for therapy. By "brute force" treatment of type 2 diabetes patients with large doses of insulin, we can overwhelm the insulin resistance and control the blood sugar, but at what price? Is it possible that high doses of insulin further enhance hepatic triglyceride synthesis and increase lipotoxicity? It seems preferable to search for new agents that will improve insulin sensitivity in the pathway that leads to suppression of hepatic gluconeogenesis and enhanced peripheral glucose uptake. With such an agent, insulin levels should fall, hepatic SREBP-1c levels should decline, and lipotoxicity should be averted. This lesson and several others may be drawn from the recent studies of the paradox of selective insulin resistance in the liver.

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