



# Indirect Regulation of Endogenous Glucose Production by Insulin: The Single Gateway Hypothesis Revisited

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**On the basis of studies that investigated the intraportal versus systemic insulin infusion and transendothelial transport of insulin, we proposed the “single gateway hypothesis,” which supposes an indirect regulation of hepatic glucose production by insulin; the rate-limiting transport of insulin across the adipose tissue capillaries is responsible for the slow suppression of free fatty acids (FFAs), which in turn is responsible for delayed suppression of hepatic endogenous glucose production (EGP) during insulin infusion. Preventing the fall in plasma FFAs during insulin infusion either by administering intralipids or by inhibiting adipose tissue lipolysis led to failure in EGP suppression, thus supporting our hypothesis. More recently, mice lacking hepatic Foxo1 in addition to Akt1 and Akt2 (L-AktFoxo1TKO), all required for insulin signaling, surprisingly showed normal glycemia. Inhibiting the fall of plasma FFAs in these mice prevented the suppression of EGP during a clamp, reaffirming that the site of insulin action to control EGP is extrahepatic. Measuring whole-body turnover rates of glucose and FFAs in L-AktFoxo1TKO mice also confirmed that hepatic EGP was regulated by insulin-mediated control of FFAs. The knockout mouse model in combination with sophisticated molecular techniques confirmed our physiological findings and the single gateway hypothesis.**

It is of critical importance to understand the mechanisms controlling endogenous glucose production (EGP), as uncontrolled hyperglycemia is the hallmark of diabetes. As long ago as 1956, Levine and Fritz (1) suggested that insulin was not a direct controller of liver glucose output. Some of their cited evidence came from *in vitro* studies on isolated liver preparations. It is now clear that buffer-perfused livers are often anoxic, and inability of insulin *in vitro* to suppress liver glucose output can be interpreted as anoxia-stimulated glycogenolysis, which enhances glucose

output. Thus, efforts turned to examining insulin's effect *in vivo* via performing studies on the oxygenated liver. This was difficult experimentally because several methodological factors arose that prevented accurate assessment of EGP *in vivo* (2). These factors included impure glucose tracer (3) and modeling errors (4). When these factors were corrected, it became absolutely clear that insulin infusion during euglycemic clamp studies reduced endogenous glucose output, as measured either by arteriovenous difference across liver or by tracer dilution techniques (5). Thus, hyperinsulinemia is accompanied by suppression of gluconeogenesis and glycogenolysis.

Insulin is secreted by the  $\beta$ -cells of the pancreas and enters the liver directly via the portal vein, where it can access insulin receptors on hepatocytes. Thus, it is logical to suggest that insulin controls endogenous glucose output by a direct intrahepatic pathway (1). Yet, significant experimental data have emerged indicating that extrahepatic signals may also be important; *i.e.*, suggesting that the primary sensor for insulin is outside the liver and a secondary noninsulin signal or signals are direct regulator(s) of glucose output.

Evidence for indirect control came from experiments from our laboratory. We performed a protocol in which insulin was administered during euglycemic clamps either into a peripheral vein or directly into the portal vein of dogs. Insulin degrades approximately half of the insulin presented to it during each passage through the liver. We could therefore match systemic insulin concentrations by giving twice the dose portally as systemically. We reported that suppression of EGP during clamps was proportional to the systemic insulin concentration but was not proportional to the portal insulin concentration (Fig. 1) (6). The latter results suggested that the primary site of action of insulin to suppress EGP was not at the liver directly but at a site distant from the liver itself.

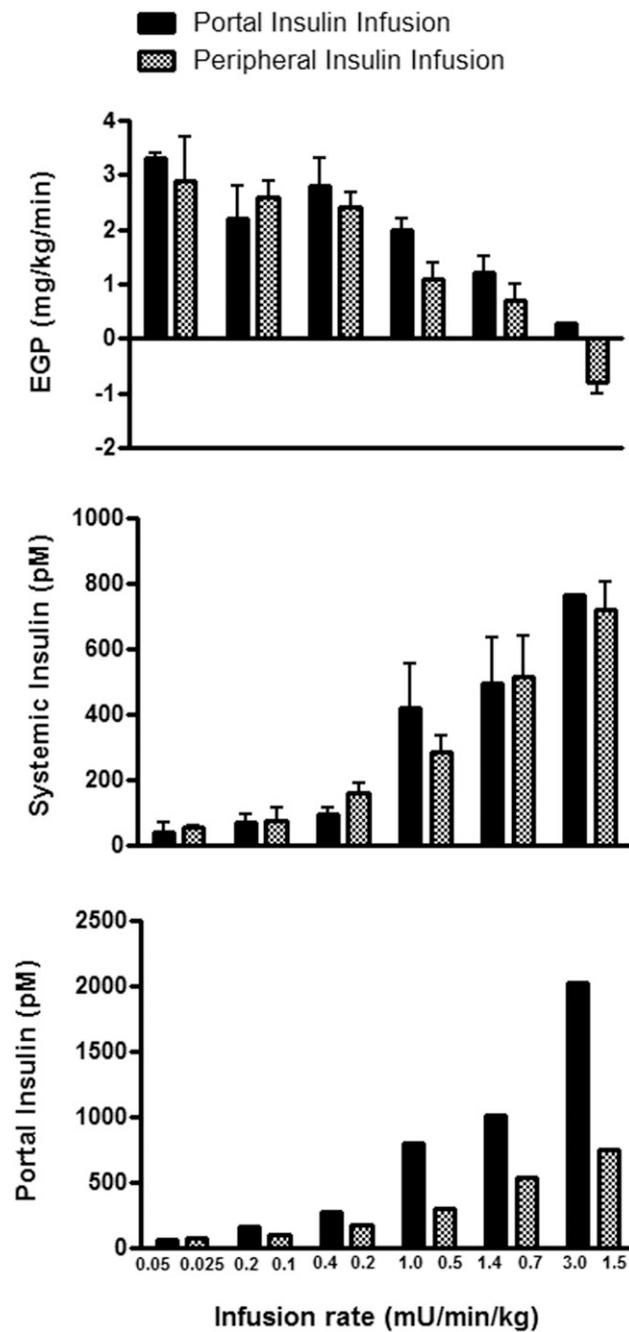
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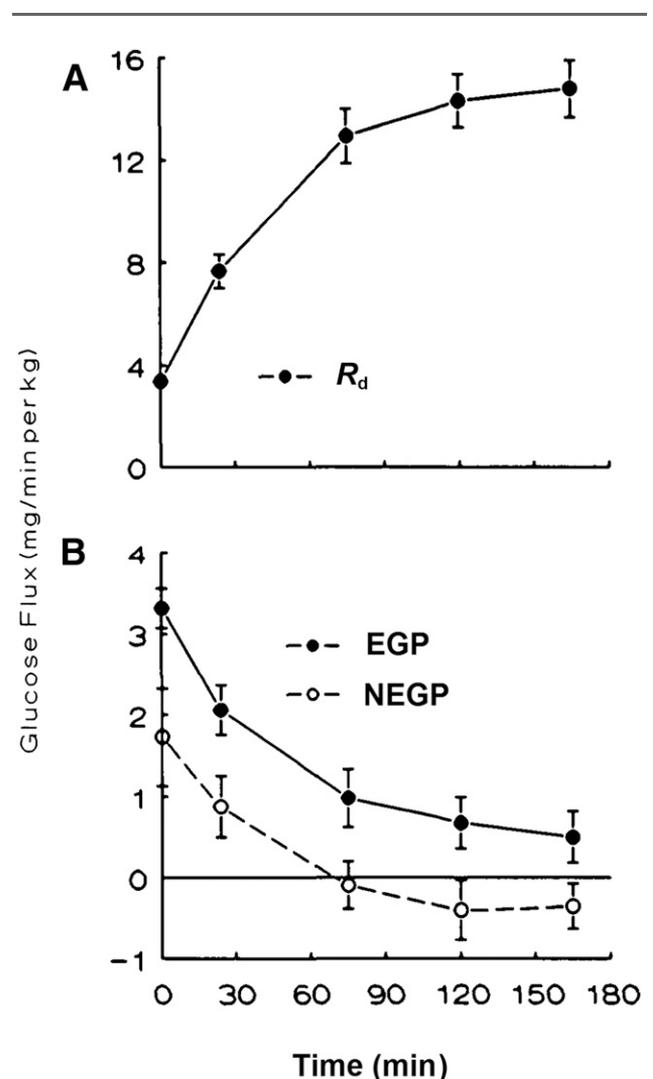


**Figure 1**—Systemic concentrations of insulin rather than portal concentrations are important to suppress EGP. Insulin infused either portally (black bars) or systemically (hatched bars) with matched systemic insulin levels was equally efficacious in suppressing EGP. Adapted with permission from Ader et al., 1990 (6).

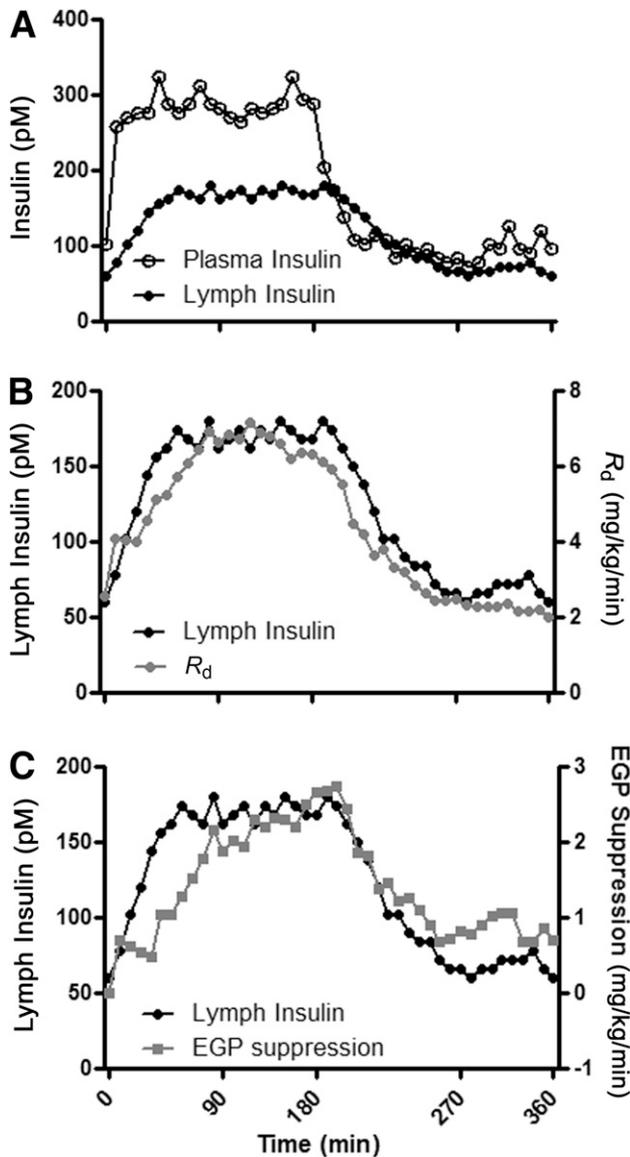
An additional set of experiments supported the notion that insulin’s action was at a site distinct from the liver. We carefully monitored the time courses of acceleration of glucose disposal during clamps and suppression of endogenous glucose output. We observed a remarkable similarity in dynamics of the increase in glucose disposal versus the suppression of glucose production, suggesting that these two actions were secondary

to a common phenomenon and rate limiting for insulin action in vivo (Fig. 2) (7).

We hypothesized that the rate-limiting step to insulin action on glucose disappearance is the slow transport of insulin across the capillary endothelium (8–10). To understand this slow time course, we examined the dynamics of glucose uptake during clamps and compared these rates to the rates of appearance of insulin in hind-limb interstitial fluid (11). We reasoned that insulin in lymph sampled from the hind limb was a surrogate measure of interstitial fluid bathing muscle tissue (11,12). We reported that the rate of appearance of insulin in the interstitial fluid during clamps was directly proportional to the rate of glucose disposal in muscle tissue and suppression of EGP and was very different from the temporal pattern of plasma insulin (Fig. 3 [10]). We therefore suggested that the transport of insulin across the capillary endothelium in muscle was rate limiting for insulin action in vivo. Over the years, we provided additional evidence for this concept;



**Figure 2**—Similarities in the rates of glucose uptake ( $R_d$ ) (A) and EGP and net EGP (NEGP) (B). Adapted with permission from Bradley et al., 1993 (7).



**Figure 3**—Average time course of plasma insulin and lymph insulin (A), rate of glucose uptake ( $R_d$ ) (B), and suppression of EGP (C) during a euglycemic-hyperinsulinemic clamp. Adapted with permission from Yang et al., 1989 (10).

for example, after injection of insulin, the retarded increase in glucose disposal is due to the time-dependent increase in interstitial hormone (9,13,14). Insulin transcytosis across the endothelium involves increased capillary recruitment (15) mediated by insulin binding to its receptors (16) on the endothelial surface. The cascade of insulin action on endothelial cells activates the IRS/PI3K/Akt pathway to release nitric oxide (17) or the Grb/Shc/MAPK pathway to release ET-1 (18) and PAI-1 (19), which induce proliferation and migration of contractile cells in addition to caveolin-mediated internalization and transport of insulin (20) from the plasma to the interstitium. We reasoned that the insulin secretory first phase evolved to overcome this tendency for slow appearance of interstitial insulin to retard the action of the hormone on glucose uptake (21).

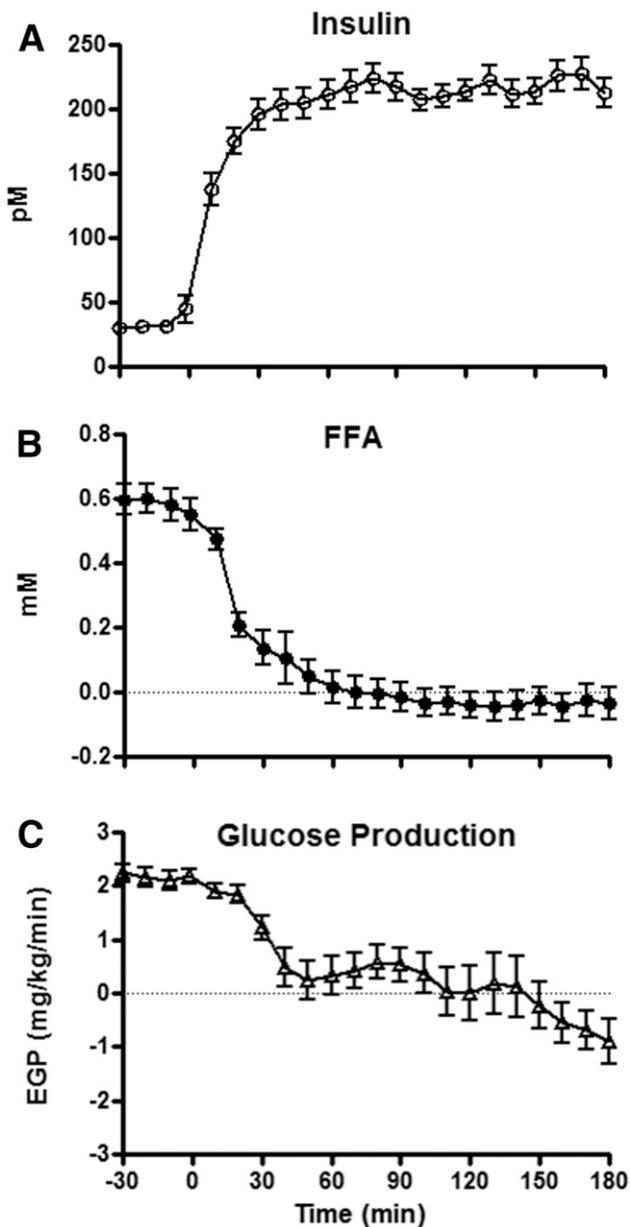
## PUTATIVE SIGNALS

The evidence that suppression of endogenous glucose output was primarily dependent on systemic (not portal) insulin and that the rate of suppression of EGP mirrored the effect of hyperinsulinemia to accelerate peripheral glucose disposal led us to look for an extrahepatic signal (or signals) that controlled liver glucose production on a moment-to-moment basis. We argued that the signal 1) must arise from an insulin sensitive tissue and 2) must be activated or inhibited only as insulin crosses the endothelial barrier.

One possible signal to control the liver directly is plasma free fatty acids (FFAs). Our first hint came from the time course of suppression of FFAs during a euglycemic-hyperinsulinemic clamp; said suppression is more rapid than suppression of EGP itself (Fig. 4). Similar to the slow appearance of insulin in the interstitium of muscle, the appearance of insulin in adipose tissue is retarded by the slow transport of insulin into the interstitium of the adipose (22,23). Thus, the concept presented itself that insulin transport into the adipose tissue is rate limiting for suppression of EGP by the liver. The latter would be true if there was a signal generated by insulin's appearance in the adipose that secondarily signaled the liver to produce glucose.

Insulin has a powerful effect to suppress lipolysis by adipose tissue (24). It therefore seemed reasonable to propose that the action of insulin to suppress glucose production occurred secondarily to suppression of lipolysis in adipose tissue, reducing plasma FFAs. Fatty acids are known to support EGP; thus, suppression of lipolysis would lower FFAs and reduce a signal for the liver to produce glucose. Because transendothelial transport of insulin was potentially rate limiting for both increasing glucose disposal by skeletal muscle and suppression of EGP, secondary to FFA lowering due to suppression of lipolysis in adipose tissue, we termed this overall mechanism the "single gateway hypothesis." The hypothesis presupposes that the slow transport of insulin across the capillary endothelium in skeletal muscle is rate limiting for glucose disposal; the slow transport of insulin across the endothelium in adipose tissue is rate limiting for the suppression of plasma FFAs and hence for the suppression of liver glucose uptake (Fig. 5).

We tested the putative role of plasma FFAs in controlling EGP with two sets of experiments. In one of the primary experiments, we interrupted the decline in FFAs during a euglycemic clamp by infusing intralipid systemically. Maintaining plasma FFAs during insulin infusion prevented the insulin-induced fall in hepatic glucose output in a clamp (25) regardless of whether the insulin was infused intraportally or systemically. In another set of experiments, we inhibited adipocyte lipolysis in vivo during euglycemic clamps using  $N^6$ -cyclohexyladenosine to find that suppression of EGP was secondary to suppression of FFAs (26). We also proposed that if FFAs are a systemic signal for EGP under control by insulin, this signal

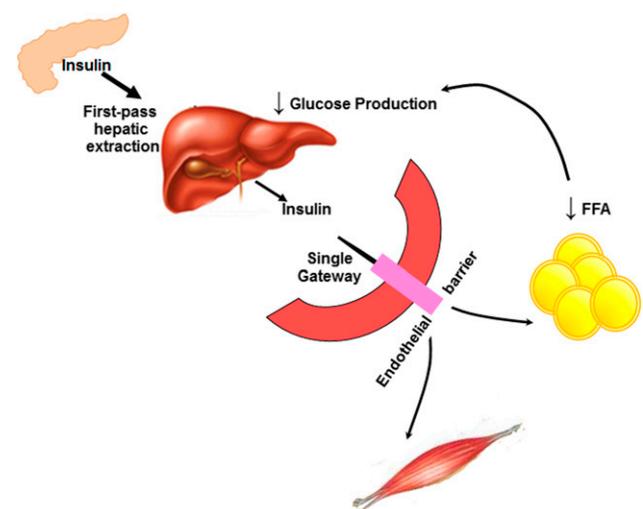


**Figure 4**—Time course of suppression of FFAs and EGP during an euglycemic-hyperinsulinemic clamp shows that suppression of FFAs is more rapid than the suppression of EGP.

would be similarly efficacious in systemic blood, as compared with blood perfusing the liver directly. We therefore used our earlier portal/peripheral protocol and compared systemic insulin infusion with insulin infused directly to the liver via the abdominal portal vein. In these experiments too the portal infusion was twice the systemic infusion to match for systemic insulin concentrations. We observed a “hand in glove” relationship between suppression of FFAs and suppression of EGP, whether insulin was infused systemically or intraportally. These results supported the concept that the insulin target for EGP suppression was extrahepatic—at the adipose tissue via FFA suppression (27).

## RECENT RESULTS SUPPORTING THE SINGLE GATEWAY HYPOTHESIS

The aforementioned work delineating the indirect role of insulin in controlling hepatic EGP via visceral adipose depot lipolysis was performed some years ago. It is only recently that two groups—Birnbaum and colleagues (28,29) and Shulman and colleagues (30)—have used sophisticated molecular techniques to provide evidence that supports the primary role of FFAs in controlling EGP. Lu et al. (28) showed that knocking out liver Akt, required for insulin signaling, leads to hepatic insulin resistance and hyperglycemia. However, deletion of Foxo1 along with hepatic Akt1 and Akt2 normalizes hyperglycemia induced by Akt knock-out alone. Because Foxo1 is the master transcription factor that regulates the expression of genes involved in hepatic glucose production such as PGC-1 $\alpha$ , PPAR- $\gamma$ , PEPCK, and G6Pase, it is reasonable to assume that redundant noninsulin-dependent pathways converge on Foxo1 to control hepatic glucose output. In another study, the same group reported that FFAs from adipose depot were responsible for hepatic glucose production even in the absence of hepatic insulin signaling pathways involving Akt and Foxo1 (29). The authors infused intralipid during a hyperinsulinemic-euglycemic clamp in liver-specific Akt1, Akt2, Foxo1 triple knockout mice (L-AktFoxo1TKO mice) to show that preventing the fall of systemic FFAs during insulin infusion prevented the fall in hepatic glucose output. They also showed that hepatic Foxo1 controlled hepatic glucose production indirectly by regulating insulin signaling and lipolysis in the adipose tissue. Further expanding on this finding, Shulman and colleagues (30) measured intrahepatic fluxes and whole-body rates of glucose turnover and lipolysis in



**Figure 5**—Single gateway hypothesis. Insulin secreted by the pancreas first passes through the liver where >50% of insulin is extracted. Insulin then crosses the endothelial barrier, which is the rate-limiting step for both glucose uptake by skeletal muscle and suppression of FFAs by the adipose tissue. Suppression of plasma FFAs acts as a signal to suppress hepatic glucose production.

L-AktFoxo1TKO mice during intralipid-infused euglycemic-hyperinsulinemic clamps to demonstrate that insulin-mediated inhibition of lipolysis in the adipose tissue leads to reductions in pyruvate carboxylase flux and hepatic acetyl CoA, which in turn suppresses hepatic EGP under normal conditions. They also showed that insulin resistance induced by infusion of proinflammatory cytokine IL-6 leads to reduced suppression of adipose tissue lipolysis, which in turn leads to increases in hepatic acetyl CoA content, EGP, and hyperglycemia.

It is important to note that the single gateway hypothesis describes moment-to-moment regulation of hepatic EGP. Data from primary hepatocytes and liver insulin receptor knockout (LIRKO) mice, in contrast, suggest a chronic effect of insulin on liver glucose production and the enzymes involved. Chronic hyperinsulinemia observed in LIRKO mice (31), as well as in vitro chronic exposure to hyperinsulinemia (32), downregulates insulin signaling via Akt and Foxo1 and stimulates EGP; this effect is exacerbated by palmitate treatment in cultured hepatocytes (33). LIRKO mice also exhibit severe peripheral insulin resistance (34), which may be responsible for increased delivery of FFAs to the liver and hyperglycemia. Hepatic Foxo1 and adipocyte triglyceride hydrolysis (29) interaction may also be responsible for increased gluconeogenesis in LIRKO mice, a phenomenon that cannot be studied in isolated hepatocyte cultures.

Hepatic Foxo1 has been discovered to play a pivotal role in the regulation of EGP by promoting anaplerotic reactions through pyruvate carboxylase flux to gluconeogenesis and suppressing hepatic glucose uptake (35,36). FFAs interact with hepatic Foxo1 to stimulate gluconeogenesis (37) possibly by increasing hepatic acetyl CoA, pyruvate carboxylase activity, and conversion of pyruvate to glucose (38,39); stimulate glycogenolysis (37); and inhibit glucose uptake, glycolysis, carbohydrate oxidation, and glycogen synthesis (40).

Induction of insulin signaling in the brain has also been shown to suppress hepatic EGP (41–43) mainly by activation of mediobasal hypothalamic  $K_{ATP}$  channels (44) independent of circulating insulin. Similarly, activation of the melanocortin pathway in the cerebral third ventricle suppresses EGP and reduces body fat mass (45). It is possible that central signaling regulates FFA release and its interaction with hepatic Foxo1 and glucose production. In a recent study, we also demonstrated that renal sympathetic nerves regulate hepatic EGP by via Foxo1 (46) possibly through central integration of neuronal signals.

On the basis of the LIRKO, LIRFKO, and L-AktFoxo1TKO data and our physiology data, we hypothesize that plasma insulin and hepatic Foxo1 communicate with adipose tissue to regulate FFA release that indirectly controls moment-to-moment hepatic EGP, with the rate-limiting step being insulin's transport across the adipose tissue capillary endothelium. Studies by the Birnbaum and colleagues (28,29) and Shulman and colleagues (30) underscore our initial findings and support the single gateway hypothesis. These

data also reiterate the importance of FFAs as an important mediator of carbohydrate metabolism between the visceral adipose depot and the liver.

### IMPORTANCE OF THE SINGLE GATEWAY—CONTROL OF THE LIVER VIA FFAS

Because overproduction of glucose by endogenous mechanisms is a primary defect in the development of type 2 diabetes, it is important to understand the underlying mechanisms. Studies of hepatic insulin resistance go back many decades, yet the simple interorgan communication underlying it has remained controversial. As outlined in this review, in vivo experiments going back several decades and supported by very new results using sophisticated molecular techniques from two leading laboratories lead to the conclusion that moment-to-moment control of glucose output by the liver is mediated by insulin suppression of lipolysis in the adipose tissue and a concomitant reduction in plasma FFAs. As reviewed above, this mechanism is consistent with the effect of insulin to be limited in time by slow transport of insulin into the adipose tissue and delayed suppression of lipolysis. Lower FFAs result in reduced glucose production. This mechanism could potentially offer a new locus for diabetes treatment. It could also be important to focus on insulin's effect on the adipose depots. Enhancing the effect to suppress lipolysis could be a more efficacious means of normalizing glycemia than affecting the liver directly. Further studies should be focused on affecting this lipolytic pathway. In any event, it is interesting that bringing together classic physiological experiments with modern molecular techniques appears to have resulted in a common understanding of this very important insulin effect and possibly a new perspective of insulin resistance.

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