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Blocking the Entrance to Open the Gate

Patrick Schrauwen,[1] Silvie Timmers,[1] and Matthijs K.C. Hesselink[2]

Almost 80% of postprandial glucose uptake resides in skeletal muscle (1). Hence, development of skeletal muscle insulin resistance is a hallmark of type 2 diabetes. Muscle is an ambiguous organ with respect to substrate selection. To fuel muscle contraction, both glucose and fatty acids can be oxidized. Glucose first needs to enter the muscle cells via insulin-mediated GLUT4-dependent transmembrane transport and then be converted to acetyl-CoA via the pyruvate dehydrogenase (PDH) complex. Oxidation of fatty acids, especially long-chain fatty acids, requires mitochondrial entrance via carnitine palmitoyltransferase-1 (CPT-1) prior to subsequent β-oxidation. To explain the well-known relationship between obesity and type 2 diabetes, Sir Philip Randle (2) proposed in 1963 that high uptake of fatty acids in skeletal muscle resulting from high free fatty acid levels observed in obesity would result in high fatty acid oxidation rates (Fig. 1). In turn, this would reduce glucose oxidation, thereby rendering the muscle insulin resistant. At the cellular level, high rates of fatty acid oxidation would result in accumulation of acetyl-CoA and citrate, thereby inhibiting PDH and glycolysis, ultimately resulting in reduced glucose oxidation. However, in the previous 2 decades, the concept of the Randle cycle in skeletal muscle has been challenged. Elegant studies by Shulman and colleagues (3–5) showed that in type 2 diabetes, reduced uptake of glucose due to compromised GLUT4 translocation, not a reduced glycolytic flux, is the main culprit in development of skeletal muscle insulin resistance. Moreover, fat accumulation in muscle, and particularly accumulation of muscle diacylglycerol (DAG), was suggested to impair GLUT4 translocation in type 2 diabetes (6). Hence, a reduced capacity to oxidize fat due to mitochondrial dysfunction (7,8) rather than high rates of fatty acid oxidation as proposed by Randle is hypothesized to underlie accumulation of triacylglycerol/DAG in muscle, thus promoting insulin resistance. Although this DAG hypothesis has dominated research on the cause of myocellular insulin resistance for some 20 years, recent studies challenge the concept that mitochondrial dysfunction is the root cause of insulin resistance (rev. in 9).

The article by Keung et al. (10) in this issue of *Diabetes* revisits the Randle hypothesis of a reciprocal relationship between fat and glucose oxidation. Inhibition of mitochondrial entry of fatty acids by oxfenicine resulted in improved glucose tolerance and insulin sensitivity in high-fat diet–fed mice, while body mass was maintained. Next, the authors confirmed that oxfenicine was indeed able to reduce fat oxidation with a concomitant increase in glucose oxidation facilitated by increased PDH activity. Interestingly, improvements in muscle glucose handling were not only observed in the basal state, but also in insulin-stimulated AKT-phosphorylation, an important marker of insulin sensitivity. Finally, GLUT4 translocation was improved.

In a completely independent study, we (11) recently reported similar findings in mice and humans who were administered with etomoxir, a pharmaceutical compound that inhibits CPT-1 and that was in clinical trials for its antidiabetic effects in the late 1990s. We found that in humans, 36 h of etomoxir administration increased glucose oxidation and GLUT4 translocation. Longer-term etomoxir administration in mice improved glucose homeostasis and insulin signaling. Together, these findings are consistent with the current results of Keung et al. (10). Furthermore, it was previously shown that mice lacking malonyl-CoA decarboxylase have elevated malonyl-CoA levels, which promote the inhibitory effect of malonyl-CoA on CPT-1, thereby leading to reduced fat oxidation and improved glucose homeostasis (12). Similarly, Koves et al. (13) showed that an increase in fatty acid oxidation can lead to incomplete oxidation of fatty acids, thereby promoting insulin resistance. In follow-up studies, Muoio et al. (14) recently showed that carnitine acetyltransferase may function to relieve pressure on the PDH complex when fatty acid oxidation rates outpace tricarboxylic acid cycle activity, and that under conditions of carnitine acetyltransferase deficiency, high fat oxidation rates may impair glucose oxidation. Collectively, these studies suggest that the essentials of the Randle cycle can operate in skeletal muscle, and that reducing myocellular fat oxidative capacity to promote insulin sensitivity is a viable approach in the treatment of type 2 diabetes.

What can we learn from these new studies? First, they show that our understanding of the mechanism(s) inducing muscle insulin resistance is not yet complete. Whereas the DAG hypothesis has attracted most attention the past few years, recent studies challenge the concept that mitochondrial dysfunction and concomitant elevated DAG lead to insulin resistance in muscle (11,15,16). Conversely, although the Randle cycle has been suggested to be of minor importance in skeletal muscle for over 3 decades, the novel results of these new studies indicate that substrate competition between glucose and fatty acids for oxidation may indeed be relevant in development of muscle insulin resistance. As is often the case, the truth may be in the middle, and both theories may prove to play a role in muscle insulin resistance. Secondly, results of Keung et al. may provide insight into new targets for diabetes treatment. It should be noted, however, that such

From the [1]Department of Human Biology, NUTRIM School for Nutrition, Toxicology and Metabolism, Maastricht University Medical Center, Maastricht, the Netherlands; and the [2]Department of Human Movement Sciences, NUTRIM School for Nutrition, Toxicology and Metabolism, Maastricht University Medical Center, Maastricht, the Netherlands.
Corresponding author: Patrick Schrauwen, p.schrauwen@maastrichtuniversity.nl.
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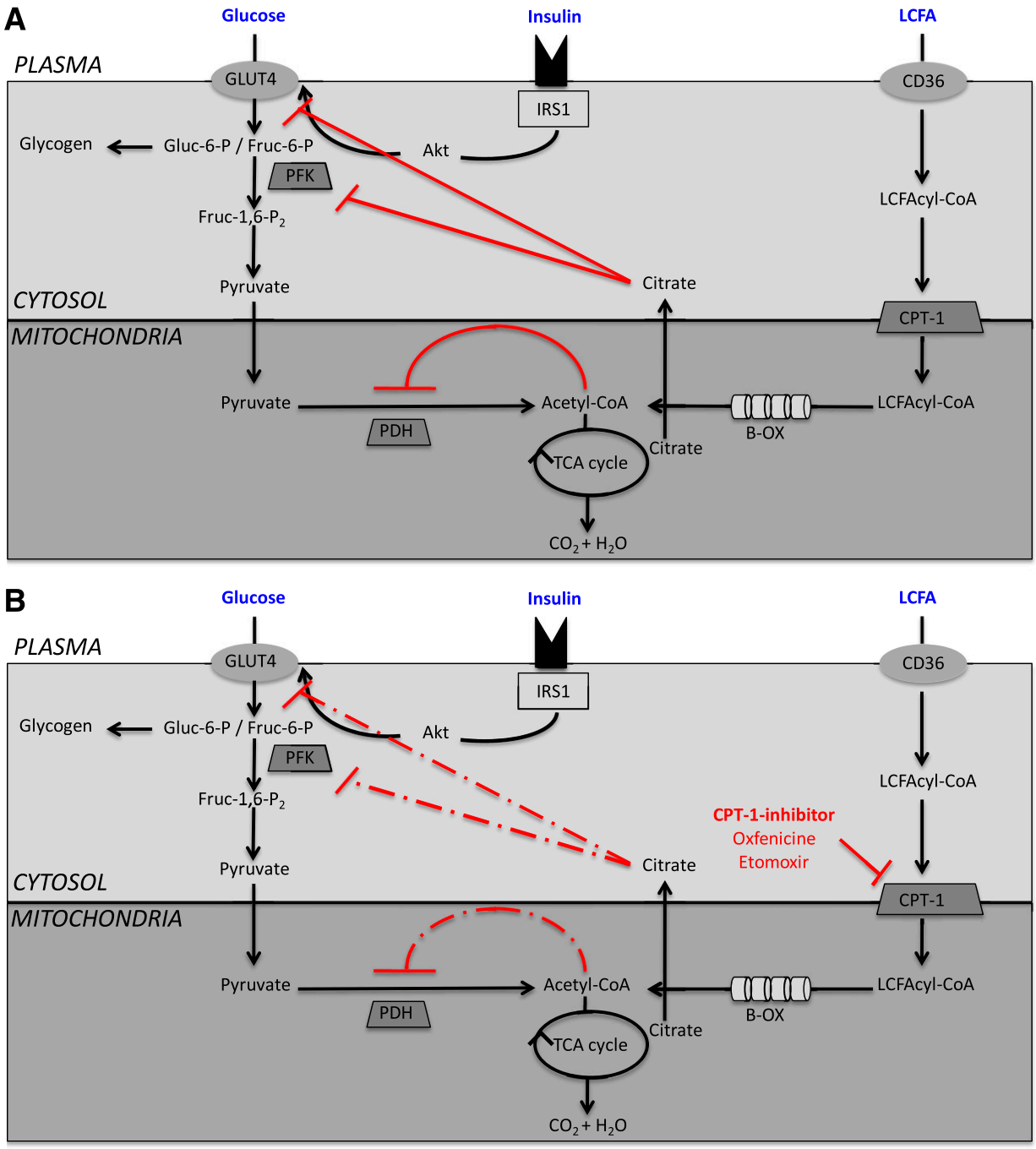

FIG. 1. Schematic representation of the reciprocal regulation of glucose utilization and fatty acid oxidation. *A*: The Randle theory proposes that high fatty acid availability and oxidation negatively affects glucose utilization, thereby contributing to insulin resistance. According to this theory, high rates of fatty acid oxidation result in the accumulation of acetyl-CoA and citrate, thereby inhibiting PDH and glycolysis at the level of 6-phosphofructo-kinase-1 (PFK), resulting in reduced glucose oxidation and hence reduced glucose uptake. PDH inhibition is caused by acetyl-CoA and NADH accumulation resulting from fatty acid oxidation, whereas 6-phosphofructo-kinase-1 inhibition results from citrate accumulation in the cytosol. These effects reroute glucose toward glycogen synthesis via glycogen synthase (GSK). *B*: Selective reduction of fatty acid oxidation (e.g., postprandial state) at the level of CPT-1 could force glucose uptake and oxidation. Keung et al. show that CPT-1 inhibition increases PDH activity, membrane GLUT4 content, and Akt phosphorylation and improves whole-body glucose tolerance and insulin sensitivity. B-OX, β-oxidation; IRS1, insulin receptor substrate 1; LCFA, long-chain fatty acid; TCA, tricarboxylic acid.

approaches are not without risk. Etomoxir has been investigated as an antidiabetic drug, but trials were abandoned because of severe side effects in nonskeletal muscle tissues. Furthermore, inhibition of fat oxidation results in increased circulatory levels of fatty acids, which increases risk of excessive fat accumulation in ectopic tissues and may thereby offset improved insulin sensitivity. At the same time, type 2 diabetes commonly coincides with reduced fat oxidative capacity (17), and it remains to be seen if a further reduction in fat oxidation is beneficial in the diseased state. Therefore, future studies— especially in humans—are required to identify the specific conditions when substrate competition is important and when fat oxidation could be a successful target to force glucose

oxidation, thereby improving glucose homeostasis. In that respect, type 2 diabetic patients are characterized by a reduced capacity to switch from fat to glucose oxidation during the transition from the fasted to fed state (18), and reducing fat oxidation—preferably by limiting fat uptake into skeletal muscle—in the postprandial state could alleviate this metabolic inflexibility. Pending the outcome of such human studies, substrate competition should be considered a putative contributor to muscle insulin resistance and hence a potential target for future intervention.

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