Fat Partitioning and Insulin Sensitivity

Robbing Peter to Pay Paul?

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The evidence is now compelling that an excess supply of fatty acids, beyond that required for energy needs, is a cause of muscle insulin resistance. Intramyocellular triglyceride accumulation is a marker of excess fatty acid supply to muscle, and it is now two decades since an association was recognized between intramyocellular triglyceride accumulation and insulin resistance (1). Arguably, the major issues now (2,3) are to first pin down the causal mechanisms between fatty acid oversupply and insulin resistance (the prevailing view is that triglycerides themselves do not cause insulin resistance because they localize within discrete lipid droplets), second, define and develop appropriate therapeutic strategies, and third, clarify the place of dysregulated lipid metabolism against other, not necessarily mutually exclusive, putative causes of insulin resistance (4).

In this issue of *Diabetes*, Wang et al. (5) have generated a novel skeletal muscle–specific lipoprotein lipase knockout$^{-/-}$mouse line (SMLPL$^{-/-}$) to better understand how lipid-derived signals integrate with insulin signaling and how reducing skeletal muscle lipoprotein lipase affects systemic fatty acid partitioning and insulin sensitivity. The studies clearly support the view that partitioning fat away from skeletal muscle reduces muscle triglyceride content and improves insulin sensitivity. This result is hardly surprising given the plethora of genetic and nutritional evidence showing that manipulation of fatty acid supply to muscle produces reciprocal changes in insulin sensitivity (2,3). For example, mice with genetically enhanced muscle lipoprotein lipase expression exhibit insulin resistance (6). However, Wang et al. were able to show that the downside of partitioning lipids away from muscle was that other tissues pay a considerable cost: the heart, liver, and adipose tissue all become insulin resistant and would most likely accumulate excessive lipids with time.

Wang et al. report a relatively mild phenotype in young SMLPL$^{-/-}$ mice. They were not obese, and plasma glucose, insulin, free fatty acid (FFA), and metabolic hormones were largely unaffected. Circulating triglycerides trended higher in the SMLPL$^{-/-}$ mice, stressing the importance of VLDL-triglyceride as a source of fatty acids for muscle but also pointing to an important contribution from skeletal muscle lipoprotein lipase action in regulating systemic triglyceride concentrations. Although whole-body insulin sensitivity was unaffected in young mice, closer examination using radiolabeled tracers revealed that skeletal muscle insulin sensitivity was enhanced, whereas white adipose tissue, heart, and hepatic insulin sensitivity were blunted, all by 50% or more—albeit without evidence of defective insulin signaling. Regarding skeletal muscle, the maneuver of restricting muscle fatty acid supply enhanced insulin sensitivity and was accompanied by enhanced insulin signaling, as indicated by increased Akt phosphorylation under insulin stimulation. This latter finding is important because it suggests that the increased insulin-mediated muscle glucose uptake is not just a result of substrate competition (i.e., adjustment of the glucose–fatty acid cycle favoring glucose metabolism). Nevertheless, the precise mediators of the increased muscle insulin sensitivity are obscure; the usual culprits linked to impaired insulin signaling when cytosolic lipids are increased include ceramides (7), diglycerides (8), and long-chain fatty acyl-coenzyme A (9); however, here they are not altered from control levels. It may be that cellular location of one or more of these species will prove important. Alternatively, others have suggested that mitochondrial lipid overload yields incomplete fat oxidation, mitochondrial distress, and insulin resistance by mechanisms that have not yet been defined (10). Whether any of these putative mechanisms are associated with the converse case of enhanced muscle insulin sensitivity above that in normal wild-type animals, as reported here in SMLPL$^{-/-}$ mice, is uncertain. One suspects this feat will not be very easy to achieve without, for example, something like an exercise training regimen.

Further phenotypic evaluation by Wang et al. (5) revealed that SMLPL$^{-/-}$ mice were more prone to obesity induced by high-fat feeding and aging, highlighting a common requirement to superimpose metabolic stress on rodent models to bring out marked phenotypic changes. Unfortunately, high-fat–fed and aged mice were not studied in the same detail as the young mice; e.g., although the young SMLPL$^{-/-}$ mice showed rates of energy expenditure similar to those of controls, this parameter needs to be examined with obesity onset. Nevertheless, the slow progression of obesity commencing from a state of selective extramuscle insulin resistance may prove a useful model to study mechanisms.

The Wang et al. (5) study highlights the importance of an often-forgotten potential source of muscle fatty acid oversupply: that derived from local lipolysis of lipoprotein-derived triglycerides mediated by lipoprotein lipase (11). Overexpression of lipoprotein lipase in either muscle (6,12) or liver (6) results in significantly increased local storage of triglyceride. Although the excess systemic fatty acids is commonly attributed to defective adipose tissue lipolysis and greater fatty acid release into the blood (13),

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the degree to which this is excessive in human insulin resistance is controversial, particularly in the presence of elevated fasting insulin levels (14). High VLDL-triglyceride levels may be more characteristic of human insulin resistance than altered FFA output (12).

The study by Want et al. raises several other major, unresolved questions. First, it remains unclear how lipid-derived signals integrate with insulin signaling in the SMLPL$^{-/-}$ model. What are the signaling pathways underpinning insulin resistance in the liver and adipose tissue when cellular lipid levels, inflammatory markers, and insulin signal transduction are not perturbed? Is it possible that signaling downstream from Akt, such as AS160/TBC1D4 activation or even Akt localization, could affect the observed biological responses (15)? Second, is the reduction in muscle triglyceride in SMLPL$^{-/-}$ mice simply mediated by reduced FFA uptake from lipoprotein triglycerides, or is fatty acid oxidation or intracellular triglyceride lipase action also enhanced? Given that peroxisome proliferator–activated receptor γ coactivator 1 (PGC1)-α mRNA was elevated in SMLPL$^{-/-}$ muscle and that PGC1 transcriptional coactivators are major regulators of several metabolic pathways (16), the potential for the integration of metabolic signals requires further study in these mice. Third, the fate of the excess triglyceride-derived fatty acids is unknown. Presumably, there is a slow accumulation in adipose and heart over time, and the study of detailed lipid turnover kinetics will be required to address this issue. Finally, an intriguing observation is the profound cardiac insulin resistance in SMLPL$^{-/-}$ mice that occurs in the absence of enhanced lipoprotein lipase activity or cardiomyopathy. In this regard, the heart exhibits an amazing potential to shift between metabolic substrate, and the reduced insulin-stimulated glucose uptake may simply result from greater triglyceride-derived fatty acids and energy substrate competition (i.e., glucose–fatty acid cycle effect).

Perhaps the major unanswered question of clinical relevance is whether providing metabolic relief by directing fat away from one tissue is a sound approach for the treatment of obesity-related disorders, such as muscle insulin resistance, or whether the ultimate fate will always be compensatory storage in other tissues and the induction of secondary complications. In the end, is such a therapeutic approach just a classic case of robbing Peter to pay Paul?

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