Regulation of Glycemic Control by Physical Activity: A Role for Mitochondria?

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Hippocrates is attributed with stating that "... eating alone will not keep a man well; he must also take exercise. For food and exercise, while possessing opposite qualities, yet work together to produce health" (1). Those words of wisdom highlight that the benefits of physical activity for maintenance of good health, in conjunction with appropriate diet, have long been recognized. As we try to manage the worldwide increase of diabetes, it is useful to remind ourselves of the value of exercise for preventing and treating insulin resistance. For adults with type 2 diabetes, both endurance and resistive exercise can lower glycated hemoglobin levels within 3–6 months (2) and moderate-intensity walking can reduce the amplitude of postprandial glucose excursions within 5–7 days (3). In the Diabetes Prevention Program, adults at risk for developing type 2 diabetes who were placed in a weight loss plus exercise program for ~3 years had significantly lower incidence of diabetes for up to 10 years after enrollment compared with those who received either standard of care or metformin (4). In the lifestyle intervention group, weight loss was the major determinant of diabetes prevention during the first year, but physical activity predicted weight maintenance and diabetes prevention in subsequent years (5). Thus, although there have been steady improvements in pharmaceutical treatments to improve glycemic control in individuals who are obese and/or diabetic, physical activity remains an important first-line therapeutic approach.

Exercise improves glucose control by increasing insulin sensitivity and non–insulin-dependent glucose uptake in skeletal muscle (6). There is also evidence that energy turnover (i.e., the oxidation of glucose and fatty acids) during muscle contraction is important for preventing the accumulation of metabolic intermediates that contribute to insulin resistance (7). Fuel oxidation leading to ATP generation occurs in the mitochondria. About 10 years ago, observations that mitochondrial content and function were reduced in individuals who were obese or diabetic lead to a hypothesis that mitochondrial dysfunction contributed to insulin resistance (8,9). Those speculations coincided with the discovery of a broad-acting transcription factor, peroxisome proliferator–activated receptor γ coactivator 1α (PGC-1α), which coordinates expression of many genes that confer an oxidative metabolic phenotype in skeletal muscle (10). Mice with muscle-specific upregulation of PGC-1α (MPGC-1α) have more muscle mitochondria and GLUT4 glucose transporters and have greater running endurance (10). Exercise training was shown to increase muscle PGC-1α expression in normal animals and humans (11,12). When it was reported that PGC-1α mRNA abundance was reduced in individuals with diabetes (13,14), it seemed plausible to expect that strategies to increase PGC-1α might also improve glucose regulation in insulin-resistant individuals. Could it be possible to develop a pill that could mimic the effects of exercise so that diabetes treatment could be delivered without having to make individuals focus as much on physical activity? So far that goal has been elusive, and some have argued that it is likely impossible given the wide-ranging effects of physical activity on multiple body systems (15). Nevertheless, understanding whether mitochondrial metabolic pathways and insulin resistance are associated in health and disease remains an important question. In the current issue of *Diabetes*, data from Summermatter et al. (16) reveal why the strategy of muscle-specific overexpression of PGC-1α has been unsuccessful for improving glycemic control in an insulin-resistant animal model.

Summermatter et al. (16) used high-fat feeding to induce insulin resistance in MPGC-1α and wild-type mice and then studied the animals after an additional 3.5 weeks of either sedentary lifestyle or treadmill exercise 3 days per week. They replicated the paradoxical prior finding (17) that sedentary MPGC-1α mice have impaired glucose tolerance, despite an increase in muscle mitochondria. Additionally, sedentary MPGC-1α mice on a high-fat diet no longer had the superior running endurance as previously shown when on normal chow (10). The novel observations provided by Summermatter et al. (16) are that *1*) insulin resistance in the sedentary MPGC-1α mice could be attributed to excess accumulation of fatty acid metabolic intermediates and reduced expression of GLUT4, *2*) insulin resistance in the MPGC-1α mice could be restored with a modest volume of exercise, and *3*) exercise training restored endurance running prowess in the MPGC-1α mice.

The MPGC-1α mice had increased expression of genes in the fat transport and oxidation pathways in their muscles; this would be expected to enhance muscle uptake of fatty acids. However, in the presence of low energy demand, the sedentary animals had evidence of incomplete fat oxidation as reflected in higher levels of acylcarnitines and sphingosine, the latter of which impaired glucose uptake in separate muscle cell culture experiments. These results are consistent with previous work showing that fatty acid metabolites could interfere with insulin action in muscle (7). The apparent reason that exercise was effective for MPGC-1α mice was that acylcarnitine and sphingosine concentrations and GLUT4 expression were restored to wild-type levels, presumably due to increased energy turnover. Therefore, this study provides evidence

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that increasing muscle mitochondrial content alone is insufficient to alter whole-body glucose control. Notably, the volume of exercise was low enough that it did not result in weight loss in either wild-type or MPGC-1α mice, which could have confounded interpretation of the results because of the separate effects of exercise and weight loss on glucose tolerance. The low exercise volume was also not sufficient to result in improved glucose tolerance or induction of mitochondrial biogenesis in the wild-type mice. Thus, the results can be largely attributed to the metabolic effects of physical activity, i.e., energy turnover in muscles, rather than the types of adaptations that would be expected if the exercise training program was continued for a longer time.

These findings confirm that in the presence of a high-fat diet, genetic or pharmaceutical treatment approaches that increase muscle fat oxidation capacity without also increasing muscle energy demand may actually exacerbate insulin resistance. This should elicit a note of caution for those who may try to develop a so-called "exercise mimetic pill." It is encouraging that the impaired glucose tolerance could be restored in the MPGC-1α mice with a modest volume of exercise. There also appears to be a synergistic effect of PGC-1α overexpression and exercise on glucose uptake in skeletal muscle that should be further explored.

Despite these intriguing findings, it remains uncertain whether targeting PGC-1α will ultimately be an effective therapeutic approach for preventing or treating insulin resistance in humans. In mice with whole-body upregulation of PGC-1α, whole-body and muscle glucose tolerance were enhanced but hepatic insulin sensitivity was reduced (18); the long-term implications for liver health are not known, but the potential for unfavorable hepatic side effects could be avoided when muscle-specific targeting of PGC-1α is used as in the current study. Yet in a recent study of mice with deficiency of PGC-1α and/or PGC-1β in skeletal muscle, mitochondrial content and exercise capacity were strongly impaired but glucose tolerance remained normal, leading the authors to conclude that PGC-1 coactivators were unnecessary for regulating insulin sensitivity in muscle (19). Other studies in mice and humans have also shown that the relationship between muscle mitochondrial functional capacity and insulin resistance is weak or nonexistent (20,21). In the current study it is important to note whole body glycemic control was only restored but not further improved in the exercising MPGC-1α animals compared with the wild-type mice. Until longer-term treatments are performed that examine the potential interactive effects of PGC-1α stimulation in combination with different exercise programs, it will not be possible to assess the full impact of these findings on diabetes prevention and treatment. Perhaps we'll find that activating PGC-1α is useful for increasing exercise ability so that individuals find it easier to lead active lifestyles, leading to better glycemic control. In the meantime, the current study provides novel insight into the regulation of muscle fuel metabolism by mitochondria and exercise and serves as another reminder of the value of leading a physically active lifestyle.

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