Do Acute Exercise and Diet Reveal the Molecular Basis for Metabolic Flexibility in Skeletal Muscle?

Bret H. Goodpaster[1] and Paul M. Coen[1,2]

In 1963, a series of elegant studies conducted by Randle et al. (1) examined the preference for fuel selection by cardiac and skeletal muscle that allowed these tissues to readily switch from glucose to fatty acid oxidation in the face of increased fatty acid availability. These seminal studies paved the way for a generation of research on mechanisms underlying preference for fuel selection in skeletal muscle and helped define specific causes of insulin resistance. More broadly, these studies also set the stage for later studies implicating an impaired capacity in insulin-resistant muscle to readily switch back and forth between glucose and fatty acid oxidation according to the appropriate conditions, described by Kelley et al. (2,3) as "metabolic inflexibility." In this issue of *Diabetes*, Constantin-Teodosiu et al. (4) further address the topic of fuel selection through examination of molecular mechanisms responsible for substrate switching, or metabolic flexibility, in humans. In these human studies using muscle biopsies in combination with high-fat diet (HFD) and exercise interventions to elicit shifts in substrate selection, the authors demonstrate a potential role for forkhead box class O transcription factor 1 (FOXO1) in HFD-mediated inhibition of pyruvate dehydrogenase complex (PDC) and glucose oxidation during exercise. The results suggest that FOXO1 may be a more important regulator of HFD-induced pyruvate dehydrogenase kinase 4 (PDK4) expression and subsequent PDC inhibition than peroxisome proliferator–activated receptor transcription factor α. Furthermore, pharmacological activation of PDC with dichloroacetate infusion alleviated the HFD-mediated inhibition of carbohydrate oxidation during exercise. The authors conclude that FOXO1, more so than peroxisome proliferator–activated receptor transcription factor α, may be an important regulator of muscle carbohydrate and fat oxidation in humans by regulating muscle PDK4 expression and consequently PDC activity, the crossroads of fat and carbohydrate metabolism.

The authors suggest that this work is potentially important to our understanding and treatment of human muscle insulin resistance because it reveals molecular changes underlying substrate switching in human muscle. They reason that PDK4 inhibition is a viable pharmacological target for treating muscle insulin resistance in obesity and type 2 diabetes. Although this may be the case, the role of PDK4 inhibition of PDC in mediating substrate switching should be considered in both physiological and pathological contexts. There is an extensive literature indicating that substrate selection from fasting to the insulin stimulated state (classic insulin resistance), is governed by different mechanisms than fuel selection during acute exercise. For example, insulin-stimulated and contraction-mediated increases in glucose uptake involve separate signaling processes (5). Further, a greater reliance on carbohydrate oxidation during acute exercise in the face of elevated plasma fatty acids may not reflect a beneficial adaptation. A classic example is the endurance-trained athlete, in whom a greater relative reliance on fatty acid oxidation (and less on carbohydrate oxidation) during acute exercise leads to preservation of carbohydrate stores, less fatigue, and greater endurance.

Although Constantin-Teodosiu et al. provide significant and compelling data regarding the potential mechanisms responsible for HFD-induced inhibition of fuel switching during acute exercise, their findings should not necessarily be extended to skeletal muscle insulin resistance. It is possible that these alterations in healthy, normal-weight subjects reflect a normal physiological response—a positive adaptation—to metabolic stressors. Similar studies should be conducted in insulin-resistant humans to determine whether FOXO1/PDK4/PDC regulation is defective in insulin-resistant muscle. Such data also raise the interesting possibility that FOXO may be a key feature of the intersection between fuel selection and anabolic action in skeletal muscle. The report by Constantin-Teodosiu et al. lays crucial groundwork to further explore the role of FOXO1, PDK4, and PDC in fuel metabolism central to insulin resistance and metabolic flexibility.

ACKNOWLEDGMENTS

No potential conflicts of interest relevant to this article were reported.

REFERENCES

1. Randle PJ, Garland PB, Hales CN, Newsholme EA. The glucose fatty-acid cycle. Its role in insulin sensitivity and the metabolic disturbances of diabetes mellitus. Lancet 1963;1:785–789
2. Kelley DE, Goodpaster B, Wing RR, Simoneau JA. Skeletal muscle fatty acid metabolism in association with insulin resistance, obesity, and weight loss. Am J Physiol 1999;277:E1130–E1141
3. Kelley DE, Mandarino LJ. Fuel selection in human skeletal muscle in insulin resistance: a reexamination. Diabetes 2000;49:677–683
4. Constantin-Teodosiu D, Constantin D, Stephens F, Laithwaite D, Greenhaff PL. The role of FOXO and PPAR transcription factors in diet-mediated inhibition of PDC activation and carbohydrate oxidation during exercise in humans and the role of pharmacological activation of PDC in overriding these changes. Diabetes 2012;61:1017–1024
5. Goodyear LJ, Kahn BB. Exercise, glucose transport, and insulin sensitivity. Annu Rev Med 1998;49:235–261

From the [1]Division of Endocrinology and Metabolism, Department of Medicine, University of Pittsburgh, Pittsburgh, Pennsylvania; and the [2]Department of Health and Physical Activity, School of Education, University of Pittsburgh, Pittsburgh, Pennsylvania.
Corresponding author: Bret H. Goodpaster, bgood@pitt.edu.
DOI: 10.2337/db12-0152

See accompanying original article, p. 1017.