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PERSPECTIVES

Exercise: not just a medicine for muscle?

John P. Thyfault[1,2,3]
and R. Scott Rector[2,3]
[1]*Research, Harry S Truman Memorial Veterans Hospital, Columbia, MO 65211, USA*[2]*Departments of Nutrition and Exercise Physiology and* [3]*Division of Gastroenterology and Hepatology, University of Missouri, CO 65211, USA*

Email: thyfaultj@missouri.edu

A sedentary lifestyle, poor dietary choices and obesity are causes of whole body insulin resistance, a pathological condition which precedes and augments the development of type 2 diabetes. Since skeletal muscle is the primary site of glucose disposal after a meal, its role in insulin resistance has received a great deal of attention; however, the role of the liver and its contribution to systemic insulin resistance cannot be ignored. In a healthy state, hepatic glucose production is increased during fasting to maintain euglycaemia, but is inhibited during a transition to postprandial conditions by increased circulating insulin. The activation of the insulin signalling pathway and a reduced activity of gluconeogenic pathways (PEPCK and G6Pase) culminates in a rapid reduction of hepatic glucose production. In contrast, when there are defects in hepatic insulin signalling, the suppression of gluconeogenic pathways is inadequate, leading to elevated glucose and insulin responses during postprandial and fasting conditions. HNF-4α, a nuclear receptor protein, and the transcription factor Foxo1 also play a role in regulating gluconeogenesis and have been targets of recent studies seeking to understand the pathology of dysregulated hepatic glucose output. Activation of HNF-4α putatively increases gluconeogenesis, while Foxo1 also augments the expression of gluconeogenic genes but is inhibited when phosphorylated by insulin-mediated activation of Akt. Evidence indicates that the interactions of Foxo1 and HNF-4α synergistically increase the expression of G6Pase, and upregulation of both factors are believed to play a role in dysregulated hepatic glucose production. Moreover, defective upstream insulin signalling results in impaired Foxo1 phosphorylation and de-activation during postprandial conditions.

Skeletal muscle has been the principal target of studies examining the acute and chronic effects of exercise to prevent or treat insulin resistance. For many decades, researchers have been studying how exercise dramatically improves insulin-stimulated glucose transport in both healthy and insulin-resistant skeletal muscle. Recent studies have begun to elucidate molecular targets in skeletal muscle that are dually and independently affected by both exercise and insulin. Although we also have known that exercise has a powerful ability to improve insulin action and control of glucose production in the liver, the molecular underpinnings for these improvements have received far less attention.

In a recent issue of *The Journal of Physiology*, DeSouza *et al*. (2010) examined the ability of an acute exercise bout to improve hepatic insulin action in two obese rodent models (*ob/ob* mice and diet-induced obese mice). The authors had the obese mice swim for 2 h and then determined if this improved hepatic insulin signalling and lowered the protein expression of HNF-4α and Foxo1 levels 8 h later. The authors report that 8 h after acute exercise hepatic insulin signalling was improved, resulting in increased phosphorylation of Foxo1, reduced content of HNF-4α, and reduced association of HNF-4α and Foxo1 proteins. Their results also suggest that these findings were dependent on improvements in insulin signalling as the addition of a PI3 kinase inhibitor abolished these effects. Thus, the authors show that a single bout of exercise can dramatically affect the molecular machinery controlling hepatic glucose production, and that these effects are dependent on enhanced insulin signalling.

Several questions remain. Although the authors showed evidence that glucose disposal was enhanced following a bout of exercise, the connection between the observed molecular changes and direct measures of reduced hepatic glucose production is needed. In addition, their study design allowed the mice to eat for a period of time after exercise resulting in a two-fold increase in hepatic glycogen above normal levels found in obese mice, leading to speculation that elevated glycogen synthesis rates may influence gluconeogenic genes. Also, would the same changes in hepatic insulin action be achieved with less stressful exercise stimuli like treadmill or voluntary wheel running or with a different duration of exercise? Furthermore, the exploration of the relationship between the presumed elevation in hepatic triglycerides and lipid intermediates normally found in obesity and exercise-induced changes in hepatic insulin signalling are warranted. As in skeletal muscle, the lipid intermediates of diacylglycerol, ceramides and others are linked to hepatic insulin resistance.

All that being said, the powerful effects of one bout of exercise to modify key proteins in the liver in an obese state should not be taken lightly, and highlight that there is much to be learned in relation to exercise and its effects on hepatic metabolism. For example, what is the stimulus by which exercise impacts hepatic insulin action? Wasserman's group has shown that manipulation of hepatic glucagon signalling dramatically impacts hepatic energy status (Berglund *et al.* 2009) similarly to exhaustive exercise. However, exercise also induces surges in other factors such as catecholimines, free fatty acids and muscle-derived IL-6, or even lactate that could play a role. The data from DeSouza *et al*. also suggest that perhaps obesity alone is not the primary defect causing hepatic insulin resistance but rather the combination of sedentary conditions and obesity that are the driving force. In fact, our group has previously shown that hepatic steatosis and whole-body insulin resistance is completely prevented by daily voluntary wheel running in a hyperphagic obese rat (Rector *et al.* 2008*b*), but an acute transition to inactivity for only 7 days results in rapid changes in lipid metabolism that precede steatosis (Rector *et al.* 2008*a*). Importantly, the changes occur in the absence of changes in adiposity or body weight. All told, further identification of how exercise positively impacts hepatic metabolism in obesity will provide a greater understanding of the pathology of hepatic insulin resistance and potential therapeutic targets. More importantly, it will continue to highlight the fact that exercise is a powerful medicine in more than just skeletal muscle.

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