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Once is enough for acute exercise benefits on insulin sensitivity

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It has been known for decades that a single exercise bout can lead to a subsequent increase in insulin sensitivity for glucose disposal (Cartee, 2015). This effect is evident a few hours after exercise cessation, and under some circumstances, it can persist for up to 48 hours. The whole body improvement in glucose disposal is largely attributable to enhanced insulin-stimulated glucose uptake by skeletal muscle. It is also well-known that individuals who regularly perform exercise (i.e., who are exercise-trained) are characterized by elevated insulin sensitivity compared to untrained individuals. A classic study by Heath et al. (Heath *et al.*, 1983) provided the initial evidence that the high level insulin sensitivity in individuals who were regular exercisers (≥ 45 minutes/day, 5-7 days/week for at least 6 months) could be lost quickly after sedentary behavior (only 10 days duration), and then essentially fully restored after performing only one exercise session. This pioneering study strongly suggested that the benefits of chronic exercise on insulin sensitivity were largely reliant of the effects of the most recent exercise session. However, the study did not directly evaluate glucose uptake by skeletal muscle or provide specific insights with regard to underlying cellular or molecular mechanisms for acute and/or chronic exercise effects on insulin sensitivity.

Several subsequent studies that evaluated both acute and chronic exercise effects on insulin sensitivity in humans relied either on detraining of habitually exercising individuals or made cross-sectional comparisons between trained and sedentary individuals. These studies also did not directly measure muscle glucose uptake, nor did they provide detailed assessment of potential mechanisms for improved insulin sensitivity.

To fill these gaps in knowledge, in this issue of *The Journal of Physiology*, Steenberg et al. (Steenberg *et al.*, 2018) compared the efficacy of a single exercise session to induce a subsequent (4 hours post-exercise) increase in insulin-stimulated glucose uptake by skeletal muscle in the same group of healthy young men under two conditions: 1) when the men were not yet regularly exercising; and 2) after they had completed a 12 week period of regular exercise training. They hypothesized that chronic exercise reduces the ability of acute exercise to increase insulin-stimulated glucose uptake. Important features of the current study included: 1) it was a longitudinal study in which the acute exercise effects were determined in the same men who were tested both prior to exercise training and after 12 weeks of training; 2) it used a one-legged acute exercise procedure that enabled simultaneous comparison between unexercised and exercised legs in the same individuals; 3) assessment of insulin-stimulated glucose uptake by muscles in each leg during a euglycemic-hyperinsulinemic clamp (EHC) using arterial-venous glucose differences with muscle blood flow

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measurements; and 4) analyzing muscle biopsies for multiple metabolic endpoints that are implicated in controlling glucose uptake.

They found that in the untrained state, greater insulin-stimulated glucose uptake in the acutely exercised leg compared to the contralateral resting control leg. In the exercise trained state, the acute effect of exercise (during EHC initiated 4 hours after one-legged exercise) was determined 48-72 hours after the final exercise training session. Insulin-stimulated glucose uptake in the rested leg was greater post-training compared to the values that were determined in the rested leg pre-training. In the post-training leg that was acutely exercised, insulin-stimulated glucose uptake was greater than the contralateral rested leg. However, the insulin-stimulated glucose uptake in the acutely exercise leg was very similar for the pre-training versus the post-training condition, i.e., chronic training plus acute exercise did not increase glucose uptake above the values with acute exercise alone. Indeed, when the delta-acute exercise effect on leg glucose uptake was calculated by subtracting glucose uptake in the resting leg from the glucose uptake in the acutely exercised leg, the delta value was lower for post-training versus pre-training. These results supported the authors' hypothesis.

Earlier experiments using rodent models performed by the same laboratory group have implicated stimulation of AMP-activated protein kinase (AMPK) as a potential part of the processes leading to enhanced insulin sensitivity after muscle contraction or exercise (Kjobsted *et al.*, 2018, Kjobsted *et al.*, 2016). AMPK is a heterotrimeric complex that can form multiple distinct combinations of the various isoforms of α , β and γ subunits. The $\alpha 2\beta 2\gamma 3$ heterotrimer complex, which is activated by acute exercise in human skeletal muscle, has been linked to enhanced insulin sensitivity in rodent muscle. In the current study, chronic exercise training resulted in elevated $\gamma 1$ isoform abundance and reduced $\gamma 3$ isoform abundance in muscle. Phosphorylation of two AMPK substrates (acetyl CoA carboxylase Ser²²¹ and TBC1D4 Ser⁷⁰⁴) was increased 2 hours after acute exercise versus the contralateral resting muscle in the pre-training condition, but not in the post-training condition. The authors interpreted these results as support for the idea that training-induced attenuation of AMPK activation may play a role in the lack of a further increase in insulin-stimulated glucose uptake after acute exercise.

In conclusion, this study was notable because it included a direct assessment of insulin-stimulated muscle glucose uptake in the same individuals several hours after acute exercise in both the untrained and trained conditions. The results demonstrated a robust enhancement of insulin-stimulated glucose uptake post-acute exercise in the untrained condition that exceeded the post-acute exercise increase in the trained condition. The study also offered intriguing evidence supporting a potential link between AMPK and insulin sensitivity in skeletal muscle after acute and chronic exercise. It is important to note that recognition of the improvement in insulin sensitivity after acute exercise in no way diminishes the many additional health benefits of exercise on metabolic, endocrine, cardiovascular, musculoskeletal and neural physiology that require chronic exercise training.

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