

Abstract

The benefits of exercise for the prevention and treatment of various diseases and overall health are well known. For instance, exercise training improves glycemic control in part due to enhanced insulin action on glucose uptake in skeletal muscle of both healthy and insulin resistant individuals. As skeletal muscle is one of the largest tissues in the human body and hence the predominant site for insulin-stimulated glucose disposal, it is essential for maintaining glucose homeostasis. In addition to the effects of regular exercise training, a single bout of exercise also improves insulin action of the prior exercised muscle due to local contraction-induced mechanisms. However, the underlying molecular mechanisms for this phenomenon are not fully elucidated. Furthermore, factors determining the magnitude of the response to a single bout of exercise on insulin action both within the muscle and at a whole-body level are not completely known. Thus the aim of the present thesis was to investigate factors important for insulin action in muscle and the enhancement of insulin action by a single bout of exercise.

In study 1, we demonstrated that the ability of muscle to enhance insulin action in response to a single bout of exercise is dependent on the training status of the muscle with a lower ability to enhance insulin action in the exercised trained state. This suggest that increased insulin action of the muscle by regular exercise training reduces the ability of a single bout of exercise to enhance insulin action further. The reduced ability to enhance insulin action in response to a single bout of exercise in the trained state was accompanied by a compromised TBC1D4 signaling likely due to a lower activation of AMPK $\alpha_2\beta_2\gamma_3$ during exercise. Thus, our findings in humans also support a role for the AMPK-TBC1D4 signaling axis in the insulin-sensitizing effect of a single bout of exercise, as previously demonstrated in rodents.

In study 2, we demonstrated that whole-body insulin action following a single bout of exercise is dependent of the insulin action in both the prior exercised muscle as well as the non-exercised muscle. As expected, exhaustive exercise of a small muscle group was found to increase insulin action in the prior exercised muscle while, surprisingly, at the same time induce systemic changes that impaired insulin action in non-exercised muscle. Due to the large amount of inactive muscles this resulted in reduced whole-body insulin action after a single bout of exercise. Thus, the magnitude of the response on whole-body insulin action following a single bout of exercise seems to be dependent on the amount of inactive vs. active muscle mass.

Lastly, using a proteomic approach we were able to identify >4000 proteins in pools of type I and type II human muscle fibers in study 3. The fibers were obtained before and after a period of endurance exercise training. The fiber type-specific database on adaptations to training provided a unique insight into muscle metabolism, which offers inspiration and possibilities for future research.

For the PhD thesis, the database was used to evaluate fiber type-specific differences in the capacity for insulin-stimulated glucose uptake in human skeletal muscle. Based on this, it was suggested that the capacity for glucose transport and glucose incorporation into glycogen was not different between fiber types, whereas the capacity for glucose phosphorylation and oxidation was higher in type I fibers. In response to training, the adaptations important for insulin-stimulated glucose uptake occurred to the same extent between fiber types.

In conclusion, the insulin-sensitizing effect of a single bout of exercise is affected by training status, non-exercised vs. exercised muscle mass and perhaps also fiber type composition and recruitment. In the present thesis, results obtained from three studies are discussed in the context of the existing literature with the purpose to elucidate the insulin-sensitizing effect of a single bout of exercise as well as factors and mechanisms contributing to this phenomenon.