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Title of project: Causal linkage of mTORC1-signaling in sensitizing muscle to insulin action in recovery from exercise

ABSTRACT

The insulin sensitivity of skeletal muscle is central for controlling glucose homeostasis and thereby avoiding development of type 2 diabetes. A single bout of exercise improves insulin sensitivity for increasing glucose uptake in the previous activated muscle. This makes the mechanism of the insulin-sensitizing effect of exercise promising as pharmacological target for patients incapable of performing exercise by natural ways. However, lack of mechanistic insight into the insulin-sensitizing effect of exercise has so far prevented the pharma-industry from taking advantage of this phenomenon. In a preliminary study, my host laboratory group have combined their expertise in conducting invasive studies in humans investigating the insulin-sensitizing effect of exercise with collaborators at the University of Sydney with expertise in advanced mass spectrometry-based phosphoproteomics. Evaluating more than 12.000 phosphorylation changes in muscle samples, thorough bioinformatic analysis identified the protein complex mammalian target of rapamycin complex 1 (mTORC1) as a potential central regulator of the insulin-sensitizing effect of exercise (unpublished data). The present PhD project aim to establish causality between mTORC1 and the insulin-sensitizing effect of exercise.

Hypothesis: mTORC1 is regulating essential mechanisms underlying improvement of insulin sensitivity towards enhancing muscle glucose uptake in recovery from exercise.

The hypothesis will be investigated with the following methods:

1) A human invasive experimental study investigating the insulin-sensitizing effect of exercise combined with pharmacological inhibition of mTORC1 in a crossover blinded design.

2) Phosphoproteomic- and extensive bioinformatic analyses of muscle biopsies will illuminate the underlying signaling network linking mTORC1 to the insulin-sensitizing effect of exercise.

Expected primary outcome: Novel insight into the extensive molecular mechanisms underlying improvement of muscle insulin sensitivity following exercise in humans. This will provide a blueprint for optimizing current and developing novel treatment options for controlling glucose homeostasis.

Expected secondary outcome: Illuminating the diverse signaling network regulated by mTORC1 in human skeletal muscle during conditions of resting, recovery from exercise and insulin stimulation.