Aspects of insulin signalling in skeletal muscle

Niels Jessen

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Official opponents: Professor Jørgen Wojtaszewski, DSi Jørgen Jensen, Norway and Jørgen Rungby.

Tutors: Sten Lund and Thomas Ledet.

Correspondance: Niels Jessen, Medical Research Laboratory, Aarhus Sygehus NBG, 8000 Aarhus C, Denmark

E-mail: Niels.Jessen@ki.au.dk

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ABSTRACT

The PhD dissertation is based on three published papers and summarizing review and is focused on mechanisms behind insulin resistance. The work was carried out in Medical Research Lab, Aarhus University Hospital and Joslin Diabetes Center, Harvard Medical School, Boston, USA. Insulin resistance in skeletal muscles is a key factor in the pathogenesis of type 2 diabetes mellitus and is in addition associated with other serious conditions like cardiovascular disease. Due to changes in life style, insulin resistance proves a major and growing challenge to the health care system world wide. In insulin resistant muscle, insulin stimulated glucose transport is impaired due to reduced translocation of glucose transporters to the cell surface. The full extent of the intracellular signalling mechanisms that connect the insulin receptor to glucose transport remains unknown, but several proteins have been identified. The activity of these proteins can be modulated by stimulators known to affect insulin sensitivity.

This dissertation aims to examine the interplay between insulin signalling proteins and modulators of skeletal muscle insulin sensitivity, demonstrated by enhancing insulin sensitivity in skeletal muscle by repetitive stimulations of the AMPK system and by inducing insulin resistance by infusion of GH. Our results show that while insulin signalling can be affected by AMPK stimulation, upregulation of the insulin signalling cascade is not necessary for improving insulin sensitivity. Furthermore, we have shown that GH stimulation does not activate the insulin signalling cascade under physiological conditions in humans in vivo, and that insulin resistance induced by short term GH infusion is not caused by impairment of the known part of the insulin signalling cascade.

These results emphasize the complexity of insulin action on skeletal muscle. Despite the growing understanding of the intracellular mechanisms involved in insulin stimulated glucose transport further research is needed to clarify the underlying causes of insulin resistance. Modulators of the currently identified proteins involved in insulin signalling are likely to play a role for both increased and impaired insulin sensitivity but do not provide a unifying explanation of insulin resistance. Further research is therefore needed in order to identify potential molecular targets for the prevention of type 2 diabetes.