Skeletal muscle insuline resistance

Mensink M, Hesselink M*, Schrauwen P
Nutrition and Toxicology Research Institute NUTRIM, Depts of Human Biology and *Movement Sciences, Maatricht University, Maastricht

Although the primary factors causing type 2 diabetes mellitus are unknown, it is well established that skeletal muscle insulin resistance plays a major role in its development. In recent years it has become evident that disturbances in skeletal muscle fatty acid metabolism can lead to muscular insulin resistance. Several studies revealed that elevated levels of intramyocellular triacylglycerols (IMTG) are tightly correlated with the severity of the insulin resistance. However, not IMTG itself, but rather accumulation of intracellular fatty acid metabolites, such as diacylglycerol (DAG), long-chain fatty acyl CoA (LCFACoA) or ceramide, are responsible for the insulin resistant skeletal muscle glucose uptake. Intramyocellular accumulation of fatty acid metabolites can either result from increased delivery to or decreased utilization of fatty acids. Indeed, we have shown that the capacity to oxidize plasma free fatty acids is reduced in diabetes and in the pre-diabetic condition of impaired glucose tolerance (IGT). In addition, in IGT subjects, this fat oxidative capacity could be improved by a combined diet and physical activity intervention program, known to reduce insulin resistance. The question remains what causes the decreased oxidative capacity? Defects in several enzymes and/or proteins have been proposed to explain this decreased oxidative capacity. However, two independent studies recently showed a coordinated downregulation of all oxidative genes in muscle of humans with diabetes. Moreover, using *in vivo* magnetic resonance spectrocopy (MRS), it was shown that mitochondrial function was impaired in insulin resistant subjects. These results point towards a phenotype of general mitochondrial dysfunction explaining the dysregulation of intramuyocellular fatty acid metabolism, rather than a defect in a single gene or protein. In this respect, it is interesting to know that exercise stimulates biogenesis of mitochondria. Furthermore, a role for thiazolidinediones in altering metabolic capacity and /or mitochondrial function is suggested explaining its beneficial effect on insulin sensitivity.

Marco Mensink, Nutrition and Toxicology Research Institute NUTRIM, Dept of Human Biology, Maastricht University, PO Box 616 6200 MD Maastricht, The Netherlands, e-mail m.mensink@hb.unimaas.nl

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