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CLINICAL PERSPECTIVES

Skeletal muscle lipotoxicity in insulin resistance and type 2 diabetes

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Patients with insulin resistance and type 2 diabetes (T2DM) commonly exhibit elevated plasma free fat acid (FFA) and muscle fat (triglyceride) levels, which may either represent inborn errors of regulation of lipid metabolism, obesity, insulin resistance of adipose tissue or defective insulin secretion with an elevated rate of lipolysis. Alternatively, accumulation of different fat species in the circulation and tissues in T2DM may occur due to an impairment of oxidation of FFAs by the mitochondria (Petersen *et al.* 2005). Since the ground-breaking studies by Sir Philip Randle documenting the substrate competition between oxidation of fat and glucose, with phosphofructokinase and pyruvate dehydrogenase enzyme activities playing a key role (Randle *et al.* 1963), the 'glucose fatty acid cycle' and elevated FFA levels have been thought to play an important role in insulin resistance. Indeed, inhibition of lipolysis and FFA levels using a nicotinic acid derivative markedly improved *in vivo* peripheral insulin action including both oxidative and non-oxidative glucose metabolism in T2DM (Vaag *et al.* 1991). The extent to which increased availability of plasma FFA levels in itself impairs proximal insulin signalling transduction in healthy subjects is controversial (Storgaard *et al.* 2004). To this end, studies have suggested various additional, parallel or complementary mechanisms by which fatty acids adversely affect muscle insulin action and glucose uptake including degree of saturation and chain length of fatty acids as well as the conversion of fatty acids to the potentially deleterious lipid species ceramide and diaglycerol. Recent data have emerged that mitochondrial overload and limited capacity of the enzyme carnitine palmitoyl-transferase-1 (CPT-1) to transport cytosolic long-chain acyl CoA into the mitochondria may be involved in the development of fat-induced insulin resistance due to the accumulation of incompletely oxidized lipid intermediates (Koves *et al.* 2008).

Studies in different tissues including muscle cell lines have suggested that FFAs may cause irreversible impairments of cellular functions by causing apoptosis, proteolysis and subsequently autophagy. However, in a recent issue of *The Journal of Physiology* an *in vivo* study by Turpin *et al.* showed that short-time intravenous fat infusion, prolonged high fat feeding or genetic obesity did not increase the expression of a number of pro-apoptotic genes or markers of autophagy (Turpin *et al.* 2009). Accordingly, in contrast to previous studies of other tissues, as well as to studies of muscle cultures *in vitro*, the study does not support the idea that FFAs cause apoptosis or autophagy in skeletal muscle.

From a clinical perspective, it makes sense that induction of apoptosis and autophagy does not belong to the most central of the rather extensive list of potential detrimental effects of FFAs on muscle functions in T2DM patients. Thus, the most severe clinical dysfunctions of skeletal muscles including insulin action induced by FFA in patients with T2DM are by nature functional, metabolic rather than structural, and most importantly at least partly reversible (Vaag *et al.* 1991). Obviously, skeletal muscle insulin resistance goes beyond reduced muscle mass in patients with T2DM, and with respect to accumulation of structural lipids in muscle *per se* as the primary cause of muscle wasting and insulin resistance, the well-known paradox of elite athletes being characterized by high insulin action and muscle mass in itself refutes that this is the case. The recent results by Turpin *et al.* support the view that factors other than lipid accumulation and lipotoxicity may play a role in the frailty related to reduced muscle mass and strength in some elderly patients with T2DM (Morley, 2008). To this end, the data from Turpin *et al.* once again indicate that extrapolations from studies in cell lines to *in vivo* whole-body physiology should be done with extreme caution.

In a recent study (also published in *The Journal of Physiology*), we challenged young healthy subjects with a diet high in fat and calories (+50%) for 5 days and found that the subjects developed severe hepatic, but not peripheral muscle, insulin resistance in response to the fat overfeeding (Brøns *et al.* 2009). Interestingly, *in vivo* muscle mitochondrial function was found not to be affected by overfeeding either. We found that increased insulin secretion preceded the development of muscle insulin resistance, challenging the general view of the pancreatic β cells sensing insulin resistance in skeletal muscle subsequently responding by increasing insulin secretion. Although 5 days of 'physiological' oral high fat feeding may also be considered a relatively short-term study resembling a feast period in many cultures, the length of the study is many times longer than the most commonly applied intravenous fat infusion studies of 3–5 h, justifying the relevance of this study set-up.

Altogether, we are faced with a scenario where short-time physiological exposure to a high-fat diet points more toward a central role of hepatic as opposed to muscle insulin resistance in the development of obesity and T2DM. Additionally, there is evidence to suggest that increased insulin secretion may actually be involved in causing the accumulation of fatty acids and triglycerides in skeletal muscle and adipose tissue. In this scenario, the role of skeletal muscle fat accumulation, lipotoxicity and in fact muscle insulin resistance *per se*, may not necessarily represent the most central role in the pathophysiological events leading to T2DM.

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