The role of ROS in insulin resistance

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(Introduced by Glenn McConell)

A great deal is known about the cellular response to starvation *via* AMP-activated protein kinase (AMPK), but less is known about the adaptation to nutrient excess. Insulin resistance is one of the earliest responses to nutrient excess, but the cellular sensors that link these parameters remain poorly defined. It has been suggested that defects in the early elements of the insulin signalling cascade constitute the major cause of insulin resistance. However, we have recently described evidence in cell and animal models as well as in insulin resistant humans that this is not the case. On the other hand, mitochondrial superoxide production is a common feature of many different models of insulin resistance in adipocytes, myotubes, and mice. Moreover, insulin resistance was reversed by agents that act as mitochondrial uncouplers, ETC inhibitors, or mitochondrial superoxide dismutase (MnSOD) mimetics. Similar effects were observed with overexpression of mitochondrial MnSOD. Furthermore, acute induction of mitochondrial superoxide production using the complex III antagonist antimycin A caused rapid attenuation of insulin action independently of changes in the canonical PI3K/Akt pathway. These results were validated *in vivo* in that MnSOD transgenic mice were partially protected against HFD induced insulin resistance and MnSOD+/− mice were glucose intolerant on a standard chow diet. These data place mitochondrial superoxide at the nexus between intracellular metabolism and the control of insulin action potentially defining this as a metabolic sensor of energy excess.