Insulin Resistance by Adiponectin Deficiency: Is the Action in Skeletal Muscle?

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Adiponectin is rapidly approaching its 20th anniversary, but it is still unclear how this apparently potent adipokine exerts its actions. The link to obesity and insulin resistance is obvious; the negative associations between plasma adiponectin concentrations and increasing fat mass or insulin sensitivity are reproducible and strong. The high abundance of adiponectin in plasma also implies a biological purpose. Adiponectin deficiency in mice gives rise to a reasonably mild insulin resistance upon high-fat feeding in most (1–3) but not all (4) models. Obviously, this fits well with the relative absence of adiponectin seen in insulin-resistant obese humans, but human monogenic causes of adiponectin deficiency are yet to be described. To further explore potential mechanisms of insulin resistance in response to adiponectin deficiency, Sweeney and colleagues (5) have used the most classic of endocrine approaches, i.e., to supplement a missing hormone or signal and observe the metabolic effect. The focus is on skeletal muscle and in particular the metabolomic patterns emerging in skeletal muscle after high-fat feeding and controlled adiponectin replenishment. Mice deficient for adiponectin were given a chow or high-fat diet for 6 weeks and received either twice daily adiponectin or saline injections. The dose of adiponectin was successfully adjusted to achieve normalization toward wild-type plasma adiponectin concentrations. After the treatment period, the mice underwent a thorough evaluation of whole-body and liver insulin resistance measurements (hyperinsulinemic-normoglycemic clamp using glucose tracers) and soleus muscle tissue was harvested for metabolomic analyses. The undirected and mass spectrometry–based metabolomic analysis of tissues was detailed and comprehensive and served the purpose of identifying patterns rather than individual molecules. The replenishment of adiponectin reversed some of the high-fat diet–induced insulin resistance, but certainly not all of it. The high-fat diet induced skeletal muscle triacylglycerol (TAG) and diacylglycerol (DAG) accumulation, and both of these accumulations were reversed by adiponectin replenishment. The significantly changing DAG species were mostly of the type that are expected to be found in the TAG synthetic pathway, whereas signaling DAG molecules, such as for example DAG 18:0/20:4, seemed to be below detection limit. Of note, there was an expected accumulation of ceramide species after high-fat feeding, but this was not reversed. Amino acid patterns were consistently reversed, whereas there was a mixed picture for intermediates in carbohydrate metabolism.

The reversal of global insulin resistance and insulin resistance–related metabolomic patterns upon adiponectin replenishment may suggest a direct action on skeletal muscle, but the evidence for that is not clear. The investigators made use of a sophisticated hyperinsulinemic-normoglycemic clamp technique in which a glucose tracer was added to specifically quantify hepatic glucose production and its suppression by insulin. Within the same experiments, this provides information about global and hepatic insulin sensitivity, where the responsiveness of glucose appearance rate to hyperinsulinemia is largely accounted for by hepatic glucose production, whereas the insulin responsiveness to glucose disappearance rate is largely dependent on glucose uptake by skeletal muscle. Although not commented on in the article, it is clear from the results that effects are seen in both liver and skeletal muscle, but the latter is by no mean the stronger one. This could imply that the adiponectin supplementation has a significant effect on hepatic insulin sensitivity, which in turn could have secondary effects on substrate delivery to skeletal muscle or even drive what is perceived as the adiponectin effect on whole-body or global insulin sensitivity.

The reversal of lipids stored in skeletal muscle after adiponectin replenishment will be the result of either reduced uptake of free fatty acid (processed into DAG and TAG) or increased oxidation of fatty acids. Several lines of evidence from the metabolomic analyses support the concept of adiponectin enhancing mitochondrial function. Adiponectin supplementation induced the coordinated decrease of acetyl-CoA and acylcarnitines and these occurred with normalization of pathological structures in the mitochondria. However, again, it is not possible to say whether this is a direct effect by adiponectin on skeletal muscle or secondary to reduced global or liver insulin resistance.

One set of molecules intimately linked to mechanisms of impaired insulin signaling did not obey to the general rule observed in this study: the accumulation of ceramides seen in response to high-fat diet was not reversed by normalization of plasma adiponectin concentrations. It was recently demonstrated that activation of adiponectin receptors is linked to a ceramidase activity (6). As intracellular ceramide concentrations could modulate a range of processes from postreceptor signaling to regulation of apoptosis, this served as unifying concept for the wide range of effects (antidiabetic, anti-inflammatory, and antiatherosclerotic) ascribed to adiponectin. The most potent reductions of tissue ceramide content in response to adiponectin receptor signaling were actually observed in the liver. In relation to the present investigation, a comparison of metabolomic patterns in response to adiponectin supplementation between skeletal muscle and liver would therefore be of significant interest, and I hope the livers have been kept for this

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purpose from this precious intervention study. In order to further dissect the issue of whether adiponectin orchestrates direct mitochondrial effects in skeletal muscle or the metabolic changes seen in skeletal muscle are secondary to events in the liver, one would need to combine the present experimental setup with that of liver or skeletal muscle–specific abrogation of adiponectin receptors (7).

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