Principal Investigator: Liu, Jiankang

LAY ABSTRACT

Summary: Insulin resistance is a cardinal feature of Type 2 diabetes, obesity and several other clinical conditions. The underlying mechanism of insulin resistance is unclear. Toxic byproducts of energy metabolism, termed reactive oxygen species, may have a causal role in multiple forms of insulin resistance. Mitochondria, the cellular component in which most energy metabolism takes place, are at once the major source and chief damage target of reactive oxygen species. The cell can replace damaged mitochondria with new, functionally fit mitochondria by the process of biogenesis. Because mitochondrial dysfunction caused by these oxidants contributes to insulin resistance and mitochondrial nutrients such as alpha-lipoic acid and acetyl-L-carnitine have been found to protect mitochondria against their insults, **we hypothesize that reducing oxidative stress by enhancing mitochondrial biogenesis by mitochondrial nutrients may prevent and/or reduce insulin resistance in diabetes.** Different mitochondrial nutrients exert their protective effects via different pathways; therefore, combinations of these compounds may have additive or synergistic effects. We propose to identify the mitochondrial nutrient combinations that are most effective in preventing and treating insulin resistance by stimulating mitochondrial biogenesis, and thus improving mitochondrial function. The proposed experiments, using both cellular and animal insulin resistance models, will examine mitochondrial dysfunction and determine the protective/remediating effects of mitochondrial nutrients, both individually and in optimal combinations. A second set of experiments will define the signal transduction pathways of mitochondrial nutrients' protective effects by focusing on improvement of mitochondrial function, especially on the enhancement of mitochondrial biogenesis. The results of these experiments may provide the basis for developing therapeutic agents to prevent and/or treat insulin resistance observed in Type 2 diabetes, obesity, and other clinical conditions.