Mitochondrial Mechanisms of Disease in Diabetes Mellitus

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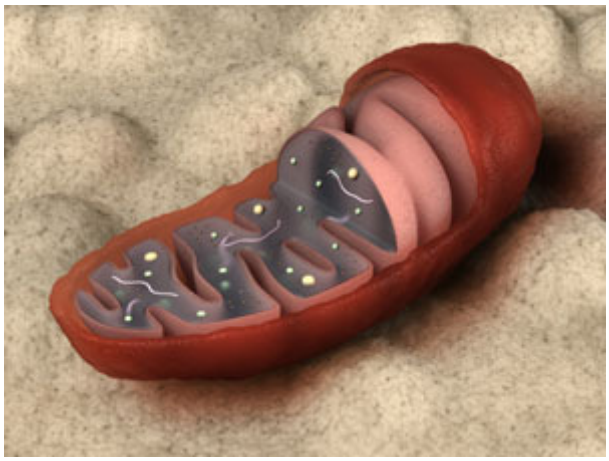
Action Points

- Much data support the concept that proper mitochondrial function is required for adequate glucose-induced insulin secretion.
- Treatment strategies that focus on increasing mitochondrial function could represent important new approaches in the treatment of diabetes.



Mitochondria are found in every cell in the human body.[1] Known as the “power plant of the cell,” mitochondria are central to the conversion of fatty acids and glucose to usable energy in the form of ATP (adenosine triphosphate).[1, 2] A growing body of evidence now demonstrates a link between various disturbances in mitochondrial functioning and type 2 diabetes.[1]

In patients with type 2 diabetes, the size, number, and efficiency of mitochondria are reduced.[3] This can have pathogenic effects in the tissues central to glucose metabolism — the pancreas, liver, and skeletal muscle.

In pancreatic beta cells, mitochondria are central to insulin secretion. As the amount of glucose in the circulation increases, so does the mitochondrial production of ATP inside the cell. When this occurs, ATP-sensitive channels open, leading to membrane depolarization and the secretion of insulin.[1]

Much data support the concept that mitochondrial function is required for appropriate glucose-induced insulin secretion.[4] Studies in beta cell lines have shown that when mitochondrial function is experimentally decreased, insulin secretion shows a similar reduction.[4] Supporting studies in humans have shown that individuals with disabling mutations in mitochondrial DNA (i.e., the A32433G mutation) demonstrate impaired pancreatic insulin secretion in response to glucose challenge.

Mitochondrial dysfunction in skeletal muscle and the liver might also contribute to the development of diabetes. As part of its cellular respiratory function, mitochondria utilize (and break down) fatty acids. When mitochondrial function is reduced, intracellular fats may accumulate.[2]

One hypothesis is that excessive accumulation of intracellular fat may have a central role in insulin resistance. This hypothesis is supported by the observation that excessive lipids lead to reductions in numbers and function of insulin receptors.[2]

The link between obesity, inactivity, and type 2 diabetes is well established — and weight loss remains a cornerstone of diabetes management.[3] The role of mitochondria as cellular “power plant” makes a compelling case for a causative relationship between mitochondrial dysfunction and clinical disease.[3]

Reduced mitochondrial capacity has been demonstrated in patients with type 2 diabetes.[3] In one study, patients who lost weight demonstrated an increase in mitochondrial density and insulin sensitivity. Patients achieved an average weight loss of 7.1% and experienced a decrease in mean HbA1c from 7.9 to 6.5, as well as significant improvements in both fasting and postprandial blood glucose.[3]

Strategies that focus on increasing mitochondrial function could represent important new approaches in the treatment of diabetes.

One agent under investigation is coenzyme Q10 (CoQ10). In animal studies, CoQ10 significantly reduced fasting and 2-hour postprandial glucose levels. In humans, early, uncontrolled studies of diabetic patients receiving CoQ10 have demonstrated improvements in blood glucose and insulin synthesis and secretion. Furthermore, the clinical benefit of CoQ10 has been evident in a number of therapeutic trials in patients with maternally inherited mitochondrial defects like MELAS (Mitochondrial Encephalomyopathy, Lactic Acidosis, and Stroke-like episodes).[1] The therapeutic advantage of supplementary CoQ10 may be especially helpful in patients taking statins, as these patients have been shown to have decreased production of endogenous CoQ10.[5]

Impaired mitochondrial function in tissues central to glucose metabolism (pancreas, muscle, liver) may be partly responsible for diabetes pathogenesis.[2] The failure to appropriately manage cellular energy needs may result in impaired insulin secretion and/or insulin resistance.[2] Targeting mitochondrial dysfunction may represent a promising path forward in the development of novel treatments for diabetes.

References:

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