

Mitochondrial function changes as we age

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(Phys.org)—A new study finds that age-related onset of type 2 diabetes and impaired glucose tolerance may be due to the lowered ability of muscle mitochondria to switch from metabolizing fatty acids to metabolizing glucose in healthy elderly people compared to young people. The study was reported in the *Proceedings of the National Academy of Sciences*.

Americans over the age of 65 are more likely to develop [type 2 diabetes](#) or [glucose](#) intolerance. The reasons for this are largely unknown, but studies have shown that muscle [insulin](#) resistance, increased intramyocellular lipid content (IMCL, triglycerides located within muscles), and decreased metabolic rates are related to aging. Because of this, scientists are interested in studying differences in the function of mitochondria located within muscle cells of elderly people compared young people.

However, singling out mitochondrial function in muscle cells has been difficult to do using typical indirect calorimetry methods. Typically, indirect calorimetry methods provide information about the whole body's basal metabolic rate, not just metabolism within muscle cells. Additionally, it is reliant on blood flow, which can change due to changes in several factors.

In an effort to gain a more accurate picture of mitochondrial function in muscle cells, Kitt Falk Petersen, Katsutaro Morino, Tiago C. Alves, Richard G. Kibbey, Sylvie Dufour, Saki Sono, Peter S. Yoo, Gary W. Cline, and Gerald I. Shulman from Yale University School of Medicine

developed a method for studying the flux of two key metabolic enzymes using liquid chromatography-tandem mass spectrometry (LC-MS/MS) and ^{13}C -labeled glucose.

During cell metabolism, pyruvate enters the mitochondria, undergoes a series of reactions that produce carbon dioxide, water and acetyl-CoA. In the first step of the process, the pyruvate reaction is catalyzed by an enzyme called pyruvate dehydrogenase. Acetyl-CoA converts to citrate through the enzyme citrate synthase. This study assessed the ratio of the flux of pyruvate dehydrogenase to citrate synthase within muscle mitochondria after a twenty-four hour fast and after insulin stimulation in healthy, non-smoking elderly subjects (average age was 69 years). They were matched with young subjects (average age was 27 years).

First, Petersen et al. did an oral glucose test and checked the subject's IMCL content. After fasting, elderly subjects had higher plasma glucose concentrations than the younger subjects, but other factors, such as insulin concentration, were the same for both. After ingestion of glucose, the concentration of glucose and insulin in plasma were found to be significantly higher in the elderly subjects. Proton magnetic resonance spectroscopy showed that IMCL content was 73% higher in elderly subjects.

After assessing the subject's [glucose tolerance](#) and IMCL content, Petersen, et al. then examined the subject's response to increased plasma insulin levels utilizing hyperglycemic-euglycemic clamp studies combined with stable isotopes of glucose. Both the young and elderly groups' insulin levels were increased while their glucose levels were kept the same by a variable infusion of glucose. Under these conditions of matched plasma glucose and increased plasma insulin concentrations elderly subjects metabolized glucose at a rate that was 25% slower than the younger subjects. This reduced rate of insulin-stimulated glucose metabolism could be attributed to reduced rates of nonoxidative glucose

disposal due to reduced activity of ATK2, an important insulin signaling protein.

Finally, the flux of pyruvate dehydrogenase and citrate synthase in muscle cells was assessed by taking muscle biopsies before and after insulin stimulation and using their LC/MS/MS technique. After fasting, fluxes for both enzymes were the same for the [elderly subjects](#) and the young subjects. This was different from the indirect calorimetry method that showed a higher respiratory quotient in the elderly group than the younger group, indicating that the elderly group had a lower metabolic rate. Their muscle-specific technique, however, was able to single-out muscle cells. Their studies showed that after fasting, both groups had a similar rate of pyruvate dehydrogenase-to-citrate synthase flux in [muscle cells](#). After insulin stimulation, the ratio of the flux of pyruvate dehydrogenase-to-citrate synthase increased three-fold in the younger [subjects](#), while the rate did not change in the elderly.

These results indicate that after insulin stimulation, the younger group switched from lipid oxidation to glucose oxidation, while this switch did not occur in the elderly group. This points to a problem in insulin signaling in the muscle associated with aging and may be a contributing factor to the higher incidence of type 2 diabetes and [glucose intolerance](#) in [elderly](#) people.

More information: "Effect of aging on muscle mitochondrial substrate utilization in humans" *PNAS*, [DOI: 10.1073/pnas.1514844112](https://doi.org/10.1073/pnas.1514844112)

Abstract

Previous studies have implicated age-associated reductions in mitochondrial oxidative phosphorylation activity in skeletal muscle as a predisposing factor for intramyocellular lipid (IMCL) accumulation and muscle insulin resistance (IR) in the elderly. To further investigate potential alterations in muscle mitochondrial function associated with

aging, we assessed basal and insulin-stimulated rates of muscle pyruvate dehydrogenase (VPDH) flux relative to citrate synthase flux (VCS) in healthy lean, elderly subjects and healthy young body mass index- and activity-matched subjects. VPDH/VCS flux was assessed from the ^{13}C incorporation from of infused $[1-^{13}\text{C}]$ glucose into glutamate $[4-^{13}\text{C}]$ relative to alanine $[3-^{13}\text{C}]$ assessed by LC-tandem MS in muscle biopsies. Insulin-stimulated rates of muscle glucose uptake were reduced by 25% (P

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