Scientists identify roots of diabetic tissue damage

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(PhysOrg.com) -- Results from comprehensive assessments of diabetes' effects on cell metabolism may aid efforts to reduce diabetic damage to nerves, blood vessels and other tissues, according to researchers at Washington University School of Medicine in St. Louis and elsewhere.

The scientists found that by blocking the sorbitol pathway, one of several pathways cells employ to use the sugar glucose, they could prevent diabetic damage to nerves and blood vessels in a rat model. Prior clinical trials of blockers for this pathway have been disappointing, according to the researchers, but they and others now think that may be because the sorbitol pathway was inadequately blocked.

"What we've found should help fine-tune efforts to slow or prevent diabetes-associated complications such as hardening of the arteries, damage to vision and loss of nerve function," says senior author Joe Williamson, M.D., retired professor of pathology and immunology. "Evidence suggests that such complications are caused by increased levels of superoxide, and our results point to the sorbitol pathway as the main source of this chemically reactive compound."

The paper appeared online in the journal *Antioxidants and Redox Signaling* and will appear in print in the future.

Normally, cells use glucose mostly to make energy through a process called glycolysis. However, as glucose levels rise, cells begin to use glucose in a process called the sorbitol pathway. The high glucose levels

associated with diabetes increase cells' use of glucose via glycolysis and the sorbitol pathway.

Both processes alter a molecule known as NAD (nicotinamide adenine dinucleotide), changing it to NADH, or NAD plus a hydrogen atom. To keep glycolysis possible, cells have to convert NADH back to NAD. If NADH levels increase relative to NAD, a metabolic imbalance occurs that can limit energy production essential for normal cell function and survival.

Pyruvate, an antioxidant produced by glycolysis, normally helps facilitate conversion of NADH into NAD. However, the sorbitol pathway does not produce pyruvate. Williamson and his colleagues theorized that when diabetes increases sorbitol pathway use, it places an increased burden on the cell by creating more NADH but leaving it with relatively less pyruvate to help change it back into NAD. They noted that a cell faced with too much NADH and too little pyruvate can turn to other enzymes to achieve the conversion, and that these enzymes produce superoxide as a product, making them an important source of diabetic tissue damage.

For the new paper, they tested the first component of this theory in a rat model of diabetes. Among other results, they found inhibiting either of two specific steps in the sorbitol pathway improved vascular function in the rats and reversed impaired motor nerve conduction velocity, or the speed at which nerves transmit electrical signals to stimulate muscles.

"It's already been established in other studies that pyruvate supplementation normalizes vascular dysfunction caused by high glucose levels and slows cataract formation in diabetic animals," Williamson says. "These results support our theories of why this happens, and others may be able to build upon this to create new and improved treatments for diabetes."

Sorbitol pathway inhibitors similar to those used by the researchers have been tested previously with disappointing results in clinical trials, but Williamson says recent studies in animals suggest those inhibitors may not have blocked the sorbitol pathway sufficiently.

"We've assembled what appears to be the most coherent explanation to date on how high glucose levels affect several different aspects of cell metabolism, and all the indicators point to the sorbitol pathway as the primary source of increased superoxide," he says. "More effective inhibitors of the sorbitol pathway are still being explored and may be able to prevent diabetic complications in the future."

For now, though, Williamson emphasizes that the best way for diabetics to prevent complications is to keep glucose levels as close to normal as possible.

Williamson also suggests that pyruvate, as a treatment for patients with poorly controlled diabetes, merits further study, but cautions that the body metabolizes pyruvate very quickly. He suggests that pyruvate may be most immediately useful in preventing diabetic damage to the eye, where it can be applied directly as eye drops and quickly reach its targets, the retina and lens.

More information: Yasuo I, Nyengaard J, Chang K, Tilton R, Kilo C, Mylari B, Oates P, Williamson J. Early neural and vascular dysfunction in diabetic rats are largely sequelae of increased sorbitol oxidation. *Antioxidants and Redox Signaling*, published online ahead of print.

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