Antioxidant treatment attenuates lactate production in diabetic nephropathy

The early progression of diabetic nephropathy is notoriously difficult to detect and quantify before the occurrence of substantial histological damage. Recently, hyperpolarized [1-13C]pyruvate has demonstrated increased lactate production in the kidney early after the onset of diabetes, implying increased lactate dehydrogenase activity as a consequence of increased nicotinamide adenine dinucleotide substrate availability due to upregulation of the polyol pathway, i.e., pseudohypoxia. In this study, we investigated the role of oxidative stress in mediating these metabolic alterations using state-of-the-art hyperpolarized magnetic resonance (MR) imaging. Ten-week-old female Wistar rats were randomly divided into three groups: healthy controls, untreated diabetic (streptozotocin treatment to induce insulinopenic diabetes), and diabetic, receiving chronic antioxidant treatment with TEMPOL (4-hydroxy-2,2,6,6-tetramethylpiperidin-1-oxyl) via the drinking water. Examinations were performed 2, 3, and 4 wk after the induction of diabetes by using a 3T Clinical MR system equipped with a dual tuned13C/1H-volume rat coil. The rats received intravenous hyperpolarized [1-13C]pyruvate and were imaged using a slice-selective13C-IDEAL spiral sequence. Untreated diabetic rats showed increased renal lactate production compared with that shown by the controls. However, chronic TEMPOL treatment significantly attenuated diabetes-induced lactate production. No significant effects of diabetes or TEMPOL were observed on [13C]alanine levels, indicating an intact glucose-alanine cycle, or [13C]bicarbonate, indicating normal flux through the Krebs cycle. In conclusion, this study demonstrates that diabetes-induced pseudohypoxia, as indicated by an increased lactate-to-pyruvate ratio, is significantly attenuated by antioxidant treatment. This demonstrates a pivotal role of oxidative stress in renal metabolic alterations occurring in early diabetes.
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