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Diabetes-induced mitochondrial changes are tissue- and model-dependent and elevated glucose levels do not activate the pathways of hyperglycemic damage in the kidney

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The development of diabetic complications has been associated with glucose-induced increased mitochondrial ROS production and subsequently activation of four major pathways described in the unifying theory such as the polyol, the hexosamine, the protein kinase C (PKC) and the advanced glycation endproduct (AGE) pathway. However, intensive glucose therapy was only beneficial for a small subset of patients. Moreover, experimental studies have not been able to clarify whether the function of the mitochondria was changed in diabetes resulting in increased ROS production. The results depended on the tissue assessed and methods used. This study therefore, used the same methods to analyze mitochondrial changes in different tissues of 3 months diabetic streptozotocin (STZ)-induced C57BL/6 and db/db mice, along with the respective age-matched controls. Diabetes-induced changes of isolated mitochondria were model, tissue and substrate specific. However, some changes were found to be independent of the diabetes type. These changes included decreased O_2 consumption in the diabetic heart as well as increased O_2 consumption and O_2^- production in the diabetic liver. Regarding the kidney of both models, ROS production remained unchanged, despite elevated renal glucose levels and increased albumin secretion in the urine. As a consequence of the absence of oxidative stress, GAPDH was not inactivated. Moreover, the PKC and the AGE pathway were not altered in the diabetic kidneys. Absence of activation of these two pathways without increase in ROS production was consistent with the unifying theory, however, ROS-independent development of albuminuria was not consistent with this theory. Moreover, it was inconsistent with the unifying theory that the hexosamine and the polyol pathway were ROS-independently activated in the STZ-model. Both pathways were not activated in the db/db model and their activation can therefore not be involved in the

development of albuminuria. As such, the unifying theory cannot explain the situation in the early phase of nephropathy. With regard to the activation of potential protective mechanism against the development of diabetic complications this study could show increased activation of NAD(P)H quinone reductase (NQO1) in the kidney of both diabetic models. Increased activity of NQO1 has previously been shown to mitigate kidney damage. However, the exact mechanisms for this activation need to be further analyzed to determine whether NQO1 mitigates diabetic kidney disease and whether it is a potential target for an anti-diabetic therapy.