Kumar Sharma

RESPONSE TO COMMENT ON SHARMA

Mitochondrial Hormesis and Diabetic Complications. Diabetes 2015;64:663–672

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I appreciate the comments of Kumar et al. (1) on my recent article (2). Although I have followed the work and insights of Michael Brownlee (3), much to my surprise our group did not find any evidence of increased mitochondrial electron transport chain (ETC) activity and superoxide production in in vivo models of diabetic kidney disease (4). To my knowledge, our group's studies are the first in vivo imaging approach to measure superoxide production in diabetic kidneys, and there was no evidence of increased mitochondrial superoxide production in the diabetic kidney using different models of diabetic kidney disease and studying the mice at early and late stages of disease. Kumar et al. (1) state, "The pathophysiology of diabetes complications should be envisioned as a series of dynamic and interrelated changes occurring over a period of time…." I fully agree with this statement; however, the authors then cite several review articles (5,6) and state that "hyperglycemia may well initially enhance mitochondrial ETC flux and increase superoxide generation…" (1). The concern is that without any new data to support the statement that mitochondrial flux is enhanced and superoxide production is increased, the authors continue on a line of reasoning that is not based on new evidence. The authors also cite other indirect data to support the Brownlee theory (3). The authors cite evidence to demonstrate that adenosine monophosphate kinase (AMPK) reduced mitochondrial reactive oxygen species (ROS) production from a review article (6) and did not cite new data from in vivo studies. It is generally accepted that studying mitochondria in mammalian cell culture may often not be relevant to in vivo mitochondrial function and should be viewed with skepticism. As noted in my Perspective article, our group did find evidence of increased ROS (i.e., H_2O_2 and other consequences of increased ROS in tissues); however, the accumulated data do not support that the primary source of increased ROS in diabetic renal tissue is from the mitochondria. I am more than willing to address new methods of measuring superoxide in real time with in vivo methods and of assessing the data with various durations of diabetes, as well as type 1 and type 2 diabetes. I agree that there may be a transient, early mitochondrial ROS production immediately after exposure to high glucose, although this was not observed with electron paramagnetic resonance studies of renal tissue from normal or diabetic kidneys (4). Until such data are available, I believe that the existing and recent data do not support the prevailing theory of mitochondrial superoxide production as the unifying theory for diabetes complications and that the in vivo data require novel explanations to determine the underlying basis for diabetes complications.

Duality of Interest. No potential conflicts of interest relevant to this article were reported.

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