Type 2 diabetes caused by reductive redox potential?

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Reactive oxygen species arise (ROS) in the mitochondria as byproducts of respiration and oxidase activity and have important roles in many physiological and pathophysiological conditions. The current literature indicate that excessive levels of ROS can cause oxidative stress and that lots of evidences link ROS and oxidative stress to the pathogenesis of type 2 diabetes mellitus (T2DM) and development of complications. Several studies have shown elevated extra- and intracellular glucose concentrations result in oxidative stress both in animal models of diabetes and in diabetic patients [1]. And ROS can contribute to the development and progression of diabetes and related complications by directly damaging DNA, proteins, and lipids or indirectly activating a number of cellular stress-sensitive pathways to induce damage to tissues such as islet β cells [2].

Recently, Waston put forward a new hypothesis, that is, some diseases including diabetes, dementias, cardiovascular disease, and some cancers are accelerated by failure of the endoplasmic reticulum to generate sufficient oxidative redox potential for forming disulphide bonds and further stabilizing the 3D conformation of physiologically active proteins [3]. It is worth noting that Waston presented the new hypothesis based on the following studies: (i) A 2009 German study showed that consumption of physiological amounts of the antioxidants vitamin C and vitamin E abrogated the capacity of physical exercise to make insulin more effective in lowering blood sugar; (ii) some patients with

severe deficiency of antioxidants including oxidative damage in tissues such as skin maintain supranormal insulin sensitivity even if they are obese; (iii) multiple studies report that the membranous sacs of the endoplasmic reticulum of insulin-resistant rodents contain much higher proportions of unfolded polypeptides and many fewer S–S bonds than does normal endoplasmic reticulum; (iv) especially, physical exercise generating large numbers of ROS is already considered by much of the diabetic medical community as the most effective first route to lowering blood sugar concentrations, not metformin.

Now, it is concluded that ROS have important physiological function in regulating glucose metabolism, and Watson's hypothesis will broaden our understanding about the role of oxidative stress in diabetes. However, some studies need to be further investigated: (i) How do ROS control glucose homeostasis? (ii) Whether insulin-signaling-pathway molecules exist in unfolded status in T2DM? And what about the ratio of unfolded protein? (iii) How the redox balance is broken in T2DM? (iv) What about the duration and frequency for exercise to prevent T2DM? What kind of combination of diet and exercise for T2DM treatment is reasonable? (v) How to explain the apparent paradox of metformin actually seems to interfere with the beneficial effects of exercise in patients with diabetes? All in all, lots of questions about oxidative redox potential and diabetes are required to clarify in the future.

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