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Combating oxidative stress in diabetic complications with Nrf2 activators: how much is too much?

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Abstract

Diabetes is increasing at an alarming rate and, despite anti-hypertensive and insulin therapies, diabetic patients are still at risk of developing complications such as chronic kidney disease, cardiovascular disease, and retinopathy. There is therefore an urgent need for more effective therapies to prevent the development and progression of diabetic complications. Oxidative stress is a major player in the aetiology of diabetic complications. However, results from clinical trials thus far using general antioxidants have been disappointing. Mechanism-based antioxidants have gained considerable attention due to their more targeted approach at reducing oxidative stress and associated complications in diabetes. The transcription factor, NFE2-related factor 2 (Nrf2), is a master regulator of redox homeostasis and the cellular detoxification response. Instead of relying on a single antioxidant, activation of Nrf2 results in the concerted upregulation of several antioxidant enzymes and cytoprotective genes, making it an attractive therapeutic target for diabetic complications. Several Nrf2 activators have been discovered and have proven effective at activating Nrf2 signalling through different mechanisms in both in vitro and in vivo models of diabetes. This review will address some of the most promising and well-known Nrf2 activators and their roles in preventing the development and progression of diabetic complications. Challenges facing the advancement of this drug class into the clinic will be discussed, as will be the future of Nrf2 activation as a therapeutic strategy in preventing the development of diabetic complications.

KEYWORDS: Antioxidant defence; Diabetes-associated atherosclerosis; Diabetic complications; Diabetic nephropathy; Mouse models; Nrf2 activators; Oxidative stress

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