Can allopurinol improve retinopathy in diabetic rats? Oxidative stress or uric acid; Which one is the culprit?

Abstract

Allopurinol, an inhibitor of xanthine oxidase, reduces both plasma uric acid and oxidative stress and shows useful effects on some complications of diabetes. However, it is not defined which of the above mentioned properties are involved. Moreover, to the best of our knowledge no study has been done on the effects of allopurinol on diabetic retinopathy. In the present study, the effect of allopurinol on experimental diabetic retinopathy and its possible mechanism has been investigated. Thirty two rats were divided into four groups of eight rats each; (1) normal, (2) diabetic control, (3) diabetic + allopurinol (50 mg/kg.day), (4) diabetic + benzbromarone (10 mg/kg.day). Drugs were administered daily and orally from the day after diabetes induction for eight weeks. Thereafter retinal function and structure were evaluated by electroretinography and microscopic studies. Uric acid and oxidative stress biomarkers were measured biochemically. Diabetes significantly increased plasma uric acid and oxidative stress markers and reduced body weight and amplitude of electroretinogram (ERG) b-wave and oscillatory potentials. Treatment of diabetic rats with allopurinol caused a significant increase in the amplitude of ERG b-wave (87%) and decrease in blood sugar (20%), uric acid (49%), and 8-iso-prostaglandin F2a (56%), but had no effect on the number of retinal ganglionic cells and oscillatory potentials. Benzbromarone showed no significant effects on the considered parameters except the reduction of uric acid. Allopurinol improved the b-wave amplitude of diabetic rats. It seems that this beneficial effect is due to the reduction of oxidative stress rather than its effect on plasma uric acid. Goharinia Mohsen 1 Department of Pharmacology, Faculty of Medicine, Shiraz University of Medical Sciences, Shiraz Zareei Athar 2 Department of Ophthalmology, Faculty of Medicine, Shiraz University of Medical Sciences, Shiraz Rahimi Mansour 3 Department of Ophthalmology, Faculty of Medicine, Shiraz University of Medical Sciences, Shiraz Mirkhani Hossein 4 Department of Pharmacology, Faculty of Medicine, Shiraz University of Medical Sciences; Medicinal and Natural Products Chemistry Research Center, Shiraz University of Medical Sciences, Shiraz Liu X, Zhu B, Zou H, Hu D, Gu Q, Liu K, et al. Carbamylated erythropoietin mediates retinal neuroprotection in streptozotocin-induced early-stage diabetic rats. Graefes Arch Cln Exp Ophthalmol. 2015;253:1263-1272. Cai X, McGinnis JF. Diabetic retinopathy: animal models, therapies, and perspectives. J Diabetes Res. 2016;2016:3789217. Behl T, Kaur I, Kotwani A. Implication of oxidative stress in progression of diabetic retinopathy. Surv Ophthalmol. 2016;61:187-196. Lorenzi K, Oates PJ. The polyol pathway and diabetic retinopathy. Diabetic Retinopathy: 2007;2007:610385. Kur J, Burian MA, Newman EA. Light adaptation does not prevent early retinal abnormalities in diabetic rats. Scientific reports. 2016;6. Sun JK, Keenan HA, Cavallerano JD, Asztalos BF, Schaefer EJ, Sell DR, et al. Protection from retinopathy and other complications in patients with type 1 diabetes of extreme duration: the Joslin 50-year medalist study. Diabetes Care. 2011;34:968-74. Afshari M, Larjani B, Rezaie A, Mojtahedi A, Zamani MJ, Astaneh-Asghari F, et al. Ineffectiveness of allopurinol in reduction of oxidative stress in diabetic patients; a randomized, double-blind placebo-controlled clinical trial. Biomed Pharmacother. 2004;58:546-50.