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Aldose reductase, ocular diabetic complications and the development of topical Kinostat®

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ABSTRACT

Diabetes mellitus (DM) is a major health problem with devastating effects on ocular health in both industrialized and developing countries. The control of hyperglycemia is critical to minimizing the impact of DM on ocular tissues because inadequate glycemic control leads to ocular tissue changes that range from a temporary blurring of vision to permanent vision loss. The biochemical mechanisms that promote the development of diabetic complications have been extensively studied. As a result, a number of prominent biochemical pathways have been identified. Among these, the two-step sorbitol pathway has been the most extensively investigated; nevertheless, it remains controversial. To date, long-term pharmacological studies in animal models of diabetes have demonstrated that the onset and development of ocular complications that include keratopathy, retinopathy and cataract can be ameliorated by the control of excess metabolic flux through aldose reductase (AR). Clinically the alleles of AR have been linked to the rapidity of onset and severity of diabetic ocular complications in diabetic patient populations around the globe. In spite of these promising preclinical and human genetic rationales, several clinical trials of varying durations with structurally diverse aldose reductase inhibitors (ARIs) have shown limited success or failure in preventing or arresting diabetic retinopathy. Despite these clinical setbacks, topical ARI Kinostat® promises to find a home in clinical veterinary ophthalmology where its anticipated approval by the FDA will present an alternative treatment paradigm to cataract surgery in diabetic dogs. Here, we critically review the role of AR in diabetes mellitus-linked ocular disease and highlight the development of Kinostat® for cataract prevention in diabetic dogs. In addition to the veterinary market, we speculate that with further safety and efficacy studies in humans, Kinostat® or a closely related product could have a future role in treating diabetic keratopathy.

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Diabetes mellitus (DM) is a major health problem that can have devastating effects on ocular health in both industrialized and developing countries (Miyamoto et al., 2007; Paques et al., 1997). DM can adversely impact many parts of the eye ranging from the conjunctiva, cornea, iris, and lens in the anterior segment to the vitreous, retina and optic disk of the posterior segment. The clinical effects of DM on ocular tissues has been reviewed in detail (Skarbez et al., 2010). Central to minimizing the impact of DM on ocular tissues is the control of hyperglycemia, because inadequate glycemic control leads to ocular tissue changes that range from a temporary blurring of vision to permanent vision loss.

1. The biochemistry of diabetic complications

The biochemical mechanisms by which relative insulin-deficiency and C-peptidopenia (Wahren and Larsson, 2015) and consequent hyperglycemia and hyperlipidemia promote the development of diabetic complications have been extensively studied in various tissues. As a result, several networks of biochemical pathways have been identified as being particularly prominent (Aronson, 2008; Oates, 2008). These include increased metabolic flux through the sorbitol pathway with consequent osmotic (Kinoshita, 1986), oxidative (Barnett et al., 1986), pseudohypoxic (Williamson et al., 1993), methylglyoxalic (Rabbani and Thornalley, 2012), and advanced glycation endproduct (AGE) (Yan et al., 2010) stresses; elevated activities of NADPH oxidase (Jha et al., 2014), diacyl glycerol/PKC (Geraldes and King, 2010), abnormal mitochondrial (Nishikawa et al., 2000) and endoplasmic reticulum metabolism (O'Brien et al., 2014), p66Shc activation (Yang et al., 2014), hexosamine synthesis (Schleicher and Weigert, 2000) and poly-ADP ribose polymerase activation (Pacher and Szabo, 2005). Common to increased metabolic flux through these interconnected pathways and enzymes is increased oxidative and nitrative stress with the excess generation of reactive oxygen/nitrogen species (ROS/RNS).

Among these various biochemical pathways, the two-step sorbitol pathway has been the most investigated; and yet, it remains controversial still. Briefly, in this pathway, excess glucose is reduced to the sugar alcohol sorbitol by the NADPH-dependent enzyme aldose reductase (AR). In the second step sorbitol, which is considered an osmolyte, is oxidized to fructose by the NAD^+-dependent enzyme sorbitol dehydrogenase (SDH). AR has broad substrate specificity and can also reduce galactose to the sugar alcohol galactitol, but galactitol is only poorly further metabolized. In diabetic tissues that do not depend on insulin for glucose entry and that do not downregulate passive glucose transport or in galactosemic tissues, elevated extracellular hexose causes abnormally increased metabolic flux of hexose through AR, the first enzyme of the sorbitol pathway. In some tissues this leads to the intracellular elevation of the polyols sorbitol or galactitol, an event that has been shown to induce osmotic and oxidative stress through the various mechanisms mentioned above. Elevated metabolic flux through AR also causes increased turnover of NADPH, the obligatory cofactor of AR and a key component of cellular antioxidant systems (Kinoshita, 1986; Oka et al., 2012). In diabetic tissues, increased sorbitol levels also lead to increased flux through SDH which results in increased fructose levels and increased turnover of NAD^+, the obligatory cofactor of SDH. The consequent elevated cytosolic $NADH/NAD^+$ ratios inhibit nicotinamide phosphoribosyl transferase (NAMPT) which leads to reduced NAD^+-dependent deacetylase Sirt-1 activity and prolonged acetylation and expression of Early growth response 1 (Egr1) activity (Vedantham et al., 2014). Erg1 controls the gene expression of a number of transcripts that are implicated in the pathogeneses of diabetes complications, including vascular cell adhesion molecules, matrix metalloproteinases, tumor necrosis factors, and tissue factors (Fig. 1). By preventing sorbitol accumulation, inhibitors of AR (ARIs) also indirectly inhibit such downstream events resulting from increased sorbitol dehydrogenase activity. Studies on the specific inhibition of SDH with SDH inhibitors (SDHIs) have been limited in the eye because sorbitol accumulation accelerates cataract formation and because SDHIs should be irrelevant for efficacy in galactosemic animals since galactitol is poorly metabolized by SDH (Maret and Auld, 1988).