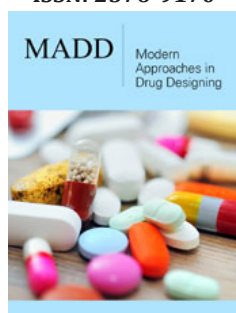


Aldose Reductase Enzyme as a Pharmacotherapeutic Target for the Treatment of Long-Term Diabetic Complications. Some Thoughts on Selectivity Issues

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Opinion

Diabetes mellitus is a group of metabolic diseases characterized by chronic hyperglycemia and disturbances of carbohydrate, fat, and protein metabolism resulting from defects in insulin secretion, insulin action, or both [1]. Diabetes mellitus (DM) is classified into four main groups: type 1 DM (T1DM), type 2 DM (T2DM), gestational diabetes, and other specific types. T1DM is characterized by the destruction of pancreatic beta (β) cells due to an autoimmune response and T2DM by the abnormal resistance of cells to the effects of insulin and the eventual dysfunction of β cells. Gestational diabetes occurs during pregnancy while the more specific types of diabetes are induced by particular events, such as new-onset diabetes after transplantation [2]. Drastic changes in lifestyle habits in the past few decades have raised the incidence of diabetes mellitus. In 2021 the prevalence of diabetes in adults ranging from 20 to 79 years worldwide was approximately 10%, representing 537 million patients, while this number is predicted to rise to 643 million by 2030 and 783 million by 2045 [3].

Once hyperglycemia occurs, patients with all forms of diabetes are at risk for developing the same chronic complications, although rates of progression may differ. Thus, long-term high glucose levels may lead to the onset of microvascular (neuropathy, retinopathy, and nephropathy) and/or macrovascular complications (coronary, cerebrovascular, and peripheral vascular diseases) as well as weak bones [2]. The enzyme that is considered responsible for diabetes' chronic complications is aldose reductase (ALR2; AR; EC 1.1.1.21; AKR1B1). ALR2 is a cytosolic enzyme localized mainly in the lens, retina, and kidney, which under normal conditions is responsible for a series of physiologic functions especially as a key component of the complex antioxidant cell defence system. ALR2 is the first enzyme of the polyol pathway, which converts glucose into sorbitol using NADPH as a co-factor. Sorbitol is slowly converted into fructose by the second enzyme of the pathway, sorbitol dehydrogenase (SDH), which uses NAD^+ as a co-factor. Normally, the polyol pathway accounts for just 3% of glucose metabolism. However, under sustained hyperglycemia in diabetic patients, the activity of ALR2 is stimulated, and this figure could rise up to 33% in tissues such as the lens, kidney, retina, and peripheral nerves. Therefore, in case of hyperglycemia, glucose is rapidly converted by ALR2 to sorbitol, which cannot easily cross membranes and accumulates into cells (osmotic stress), causing cell and tissue dysfunction. Additionally, the exhaustion of NADPH and the disturbance of NADH/NAD^+ ratio can cause oxidative stress, reductive stress (pseudohypoxia) as well as protein kinase C (PKC) stress, all of which are related to diabetic chronic complications. Furthermore, fructose, via oxidation, gives intermediates that can lead

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to advanced glycation end products (AGEs); this glycativ stress is also considered responsible for diabetes' chronic complications [4,5].

The great number of aldose reductase inhibitors (ARIs) discovered in the past 40 years shows a wide variety of different chemical structures that, however, share certain molecular features. In fact, most ARIs bear an acidic group, which is capable of effectively anchoring the inhibitor to the polar positively charged "anion-binding pocket" of the ALR2 catalytic site through ionic and/or hydrogen bonds. In addition, one or more aromatic moieties may contribute to ligand/enzyme binding by efficiently fitting the lipophilic region of the ALR2 active site including the "selectivity or specificity pocket". These latter hydrophobic interactions can function as important selectivity determinants. Up to now, two inhibitors have reached the market. Tolrestat was marketed in several countries in Europe during the 1990s, but was shortly withdrawn due to hepatotoxicity. On the other hand, epalrestat is still marketed for the treatment of diabetic neuropathy in a number of countries in Asia (e.g. Japan, India and China), and appears to be well tolerated, but it has a short half-life, and its efficiency is considered marginal. However, due to safety concerns, this drug did not get US FDA and EMA approval [6,7].

ALR2 is a member of the aldo-keto reductase (AKR) superfamily, and another member of the AKR superfamily is aldehyde reductase (ALR1; EC1.1.1.2; AKR1A1). It is believed that the unfavorable profile of many ARIs in clinical trials is due to their concurrent inhibition of these closely related AKRs [7,8].

One of the primary roles of ALR1 in diabetes (as well as of ALR2) is the detoxification of tissues from the reactive α -oxoaldehyde glycativ agents, like methylglyoxal and 3-deoxyglucosone [9-11]. However, other enzymes, such as glyoxalase-I, betaine aldehyde dehydrogenase, 2-oxoaldehyde dehydrogenase, and the dimeric dihydrodiol dehydrogenase could also act as the detoxification enzymes for these glycativ agents [12,13]. It is noted that the dimeric dihydrodiol dehydrogenase is not inhibited by the established ALR1 inhibitors (valproic acid and barbiturates) or the classical ARIs (sorbitol and tolrestat) [14]. Furthermore, kidney polyols may be generated by both aldose and aldehyde reductase, with ALR1 significantly contributing to the polyol production in the kidney cortex, the predominant site of diabetes linked kidney lesions [15]. It is noted that ALR1, but not ALR2, is localized in the kidney cortex [16]. Although a degree of selectivity toward ALR2 may be important for a successful ARI, on the basis of the above points, this selectivity feature should not be considered as a negating factor for the identification of an initial lead ARI. Overall, as research for ARIs appears to have reached a plateau, novel chemotypes are sought, that can overcome the adversities posed from the known classes of inhibitory compounds.

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