Chapter 2

Aldose Reductase Inhibitors as Potential Therapeutic Drugs of Diabetic Complications

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Additional information is available at the end of the chapter

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1. Introduction

Diabetes mellitus has become a major health threat as a global rise in it has been seen. The chronic disease has afflicted over 171 million people worldwide in 2000 and the incidence is expected to grow steadily to 366 million by 2030. As of May 2008, an estimated 92 million adults in China of the most populous country were living with diabetes and 148 million adults with prediabetes [1]. Diabetes mellitus is one of the leading causes of death across the globe particularly in the developing world. Most diabetic patients suffer from so-called long-term complications such as neuropathy, nephropathy, retinopathy, cataracts and even stroke. These complications arise from chronic hyperglycemia, which causes damage to blood vessels and peripheral nerves, greatly increasing the risk of heart attack. A number of mechanistic explanations for the complications have been proposed (for the reviews, see Refs. [2-5]). First, they include hyperactivity of polyol metabolic pathway that produces elevated accumulation of cellular sorbitol leading to osmotic stresses on cells, and is then implicated mainly in microvascular damage to retina, kidney, and nerve systems. As the second mechanism, increased formation of advanced glycation end products (AGEs) activates nonenzymatic glycosylation of proteins and lipids, and in turn leads to dysfunctional behaviors of related enzymes and receptors. The third of them is hyperglycemia-induced activation of protein kinase C (PKC) isoforms which evokes pathological changes in growth factor expression. The fourth is diverting of excess intracellular glucose into the hexosamine pathway and consequent overmodification of enzymatic proteins by N-acetylglucosamine along with abnormal enzyme behaviors. Finally, the fifth mechanism is recently proposed in which an hyperglycemia-induced impairment of antioxidant defense such as the overproduction of reactive oxygen species (ROS) readily initiates inflammation responses.

Among these mechanisms, the polyol pathway was first discovered and in fact is generally accepted to be the mechanism of prime importance in the pathogenesis of diabetic

complications. Aldose reductase (AR, EC 1.1.1.21) that is the first and rate-controlling enzyme in the polyol pathway is of importance for the pathway and in turn has been a potential target for drug design, therefore, the inhibition of aldose reductase has been an attractive approach to the prevention and treatment of diabetic complications. In line with the focus of this chapter, ARIs and their therapeutic functions will be discussed in the following sections.

2. Aldose reductase and the polyol metabolic pathway of glucose

2.1. The polyol pathway

Aldose reductase together with sorbitol dehydrogenase (SDH) forms the polyol pathway as shown in Figure 1. In the polyol pathway, AR initially catalyzes the NADPH-dependent reduction of the aldehyde form of glucose to form sorbitol. Sorbitol dehydrogenase then utilizing NAD oxidizes the intermediate sorbitol to fructose. The conversion of glucose to sorbitol catalyzed by AR was first identified in 1956 by Hers in the seminal vesicles where glucose is converted into fructose to provide an energy source for sperm [6]. Soon after, the polyol pathway sorbitol was found in diabetic rat lens by Van Heyningen [7]. In 1965, pathogenic effects of AR and its associated polyol pathway were first identified in the lens by Kinoshita, and these works formed the basis for the osmotic stress hypothesis of sugar cataract formation [8]. It proposes that intracellular excess sorbitol produced by AR accumulates in cells and is difficult to diffuse across the cell membranes, and consequently the osmotic damage to cells occurs which eventually leads to diabetic cataract complication [9]. These discoveries taken together led to the opening for studies on the pathogenic role of AR and the polyol pathway in the development of diabetic complications, and also made the beginning of research for the mechanism of diabetic complications. AR is now known to be present in most of the mammalian cells. Normally, the cellular glucose is oxidatively metabolized through the glycolysis pathway and then the Krebs cycle to produce the building blocks and energy for cells. Under hyperglycemic conditions, however, the increased amount of glucose activates AR and is metabolized by the activated polyol pathway.

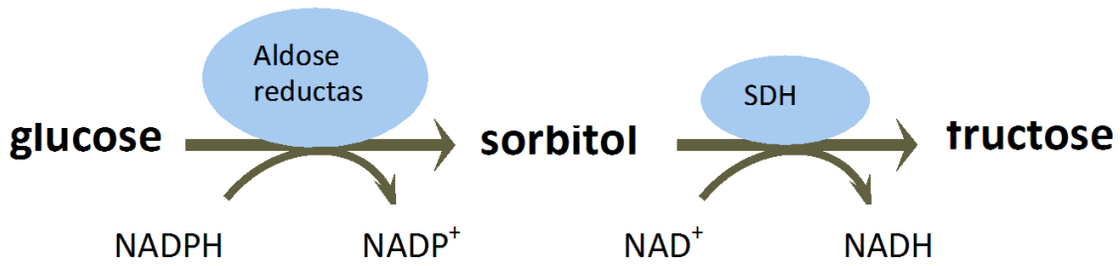


Figure 1. Polyol metabolic pathway of glucose

After finding the AR-mediated glucose metabolism, several mechanisms other than the AR-initiated polyol pathway for diabetic complications were successively proposed. Nevertheless, the polyol pathway appears still to be a compelling mechanism of diabetic

complications because growing evidences have been shown for an involvement of the abnormally activated polyol pathway in the pathogenesis of diabetic complications.

Biomolecular evidences for the role of the polyol pathway are recently provided by cellular experiments and regulations of AR gene expression in the presence of high glucose induction. The protein expression of AR, and the intracellular sorbitol and fructose contents appeared to be up-regulated in mouse Schwann cells under high glucose conditions [10, 11]. In transgenic mice with AR overexpression, an elevated accumulation of sorbitol and fructose along with a simulteneous decrease in tibial motor nerve conduction velocity were found [12]. In peripheral blood mononuclear cells from nephropathy, high glucose increased NF-kB binding activities, which in turn induced an expression of AR protein [13]. Observations in high glucose-induced rat mesangial cells suggested that altered protein kinase C activity mediated through activation of the polyol-pathway contributes to a loss of mesangial cell contractile responsiveness [14]. A particular convincing finding is that these detrimental alterations could be prevented or reversed by the treatment with AR inhibitors (ARIs).

Consistent findings can be also traced in the animals with a deficient AR gene expression. In db/db mice with an AR null mutation, diabetes-induced reduction of platelet/endothelial cell adhesion molecule-1 expression and increased expression of vascular endothelial growth factor were prevented which may have contributed to blood-retinal barrier breakdown. As a result, long-term diabetes-induced neuro-retinal stress and apoptosis and proliferation of blood vessels were less present [15]. This suggests that AR is responsible for the early events in the pathogenesis of diabetic retinopathy, leading to a cascade of retinal lesions. Also, AR-deficient mice were protected from delayed motor nerve conduction velocity, increased c-Jun NH2-terminal kinase activation, depletion of reduced glutathione, increased superoxide accumulation, and DNA damage [16]. AR-deficient or ARI-treated mice were protected from severe ischaemic limb injury and renal failure, showing only modest muscle necrosis and significant suppression of serum markers of renal failure and inflammation [17]. In addition, AR inhibition counteracted diabetes-induced oxidative-nitrosative stress and poly(ADP-ribose) polymerase activation in sciatic nerve and retina [18]. Very recently in human mesangial cells in culture, exposure to high glucose and overexpression AR increased the expression of fibronectin. This increase was prevented by the AR inhibitors sorbinil and zopolrestat. Treatment with high glucose and transfected with plasmid PcDNA3.0-AR, resulted in phosphorylation and activation of ERK, JNK and AKT signaling pathway, and an increase in the expression of fibronectin. Treatment with inhibitor of JNK and AKT signaling pathway decreased the expression of fibronectin. Obviously, AR may be linked to extracellular matrix deposition in diabetic nephropathy, which is regulated by JNK and AKT [19].

On the other hand, in streptozotocin-diabetic rats, significantly delayed motor nerve conduction velocity, decreased R-R interval variation, reduced sciatic nerve blood flow and decreased erythrocyte 2,3-diphosphoglycerate concentrations were all ameliorated by treatment with ARI [5-(3-thienyl) tetrazol-1-yl]acetic acid. The inhibitor also reduced platelet hyperaggregation activity, decreased sorbitol accumulation and prevented not only myo-

inositol depletion but also free-carnitine deficiency in diabetic nerves. Therefore, there is a close relationship between increased polyol pathway activity and carnitine deficiency in the development of diabetic neuropathy [20].

Similar to the results from cellular experiments and gene expression regulations, the role of the polyol pathway has been confirmed by animal models. Marked muscle necrosis and renal failure with accumulation of sorbitol and fructose were identified in ischaemic muscles of mice [17], and the disturbance in the renal medulla including oxygen tension, oxygen consumption, lactate/pyruvate ratio and pH were observed in diabetic rats [21]. Notably, these alterations were preventable by either ARI treatment or AR-deficient suggesting the involvement of the polyol pathway in the acute kidney injury.

Besides, the pathways of AGEs, PKC, hexosamine, and ROS can be causally linked to downstream events of the increased polyol pathway flux including alterations in cellular redox balance and fructose concentration [2, 5, 22, 23]. As described above, for example, the loss of mesangial cell contractile responsiveness in high glucose-induced rat mesangial cells resulted from the activation of the polyol-pathway could be mediated by altered PKC activity [14]. In vitro studies on cultured human mesangial cells and in vivo studies in the diabetic renal cortex of streptozotocin-diabetic rats have indicated the presence of both increased AR activity and oxidative/nitrosative stress in the pathogenesis of diabetic nephropathy, and the nitrosative stress and polymerase activation could be counteracted by AR inhibition [24]. Moreover, the increased kinase activation, depletion of reduced glutathione, increased superoxide accumulation, and DNA damage could be prevented by AR-deficiency in the amelioration of motor nerve conduction velocity [16]. Recently, osmotic stress resulting from the accumulation of sugar alcohols in lens epithelial cells which contain mitochondria, has been shown to induce endoplasmic reticulum stress that leads to the generation of reactive ROS and apoptotic signaling [25].

The polyol pathway is in fact supported by successfully therapeutic applications of ARI drugs epalrestat and tolrestat in diabetic complications such as neuropathy. Epalrestat is now on the markets in Japan, China, and India while tolrestat was marketed in several countries although it was withdrawn. Also, a few of other ARIs involving fidalrestat and ranirestat have been advanced to late stage of clinical trials.

2.2. Properties of AR

AR belongs to the aldo-keto reductase enzyme superfamily. Crystallized complexes of AR with ligands and site directed mutagenesis allowed the enzyme structure to be identified. The enzyme is a single polypeptide domain composed of 315 amino acid residues [26]. The peptide chain blocked at the amino terminus folds into a β/α-barrel structural motif containing eight parallel β strands which are connected to each other by eight peripheral α-helical segments running anti-parallel to the β sheet. The active site is located in a large and deep crevice in the C-terminal end of the β barrel, and the NADPH cofactor binds in an extended conformation to the bottom of the active site [27, 28]. However, it is likely that the active site often changes its conformational shape because a variety of binding

conformations bound by ARIs, represented by the complexes with ligands sorbinil (PDB entry code 1AH051), tolrestat (PDB entry code 2FDZ52), and IDD594 (PDB entry code 1US053), have been reported [29-32]. These ligand-dependent conformations indicate a remarkable induced fit or flexibility of the active site. Nevertheless, at least three distinct binding pockets in the active site can be proposed as shown in Figure 2 according to a number of studies on crystal structures of AR by X-ray crystallography and mutagenesis [30, 33-38]. The first is usually occupied by the anion head of ligand and thus named "anion binding pocket". It is made up of Tyr48, His110, Trp20, and Trp111 side chains and the positively charged nicotinamide moiety of the cofactor NADP+. The second is a hydrophobic pocket, known as specificity pocket, and lined by the residues Leu300, Cys298, Cys303, Trp111, Cys303, and Phe122 [30]. The specificity pocket displays a high degree of flexibility and the residues lining this pocket are not conserved in other aldo-keto reductases such as aldehyde reductase, The third is another hydrophobic pocket formed by the residues Trp20, Trp111, Phe122, and Trp219 [34].

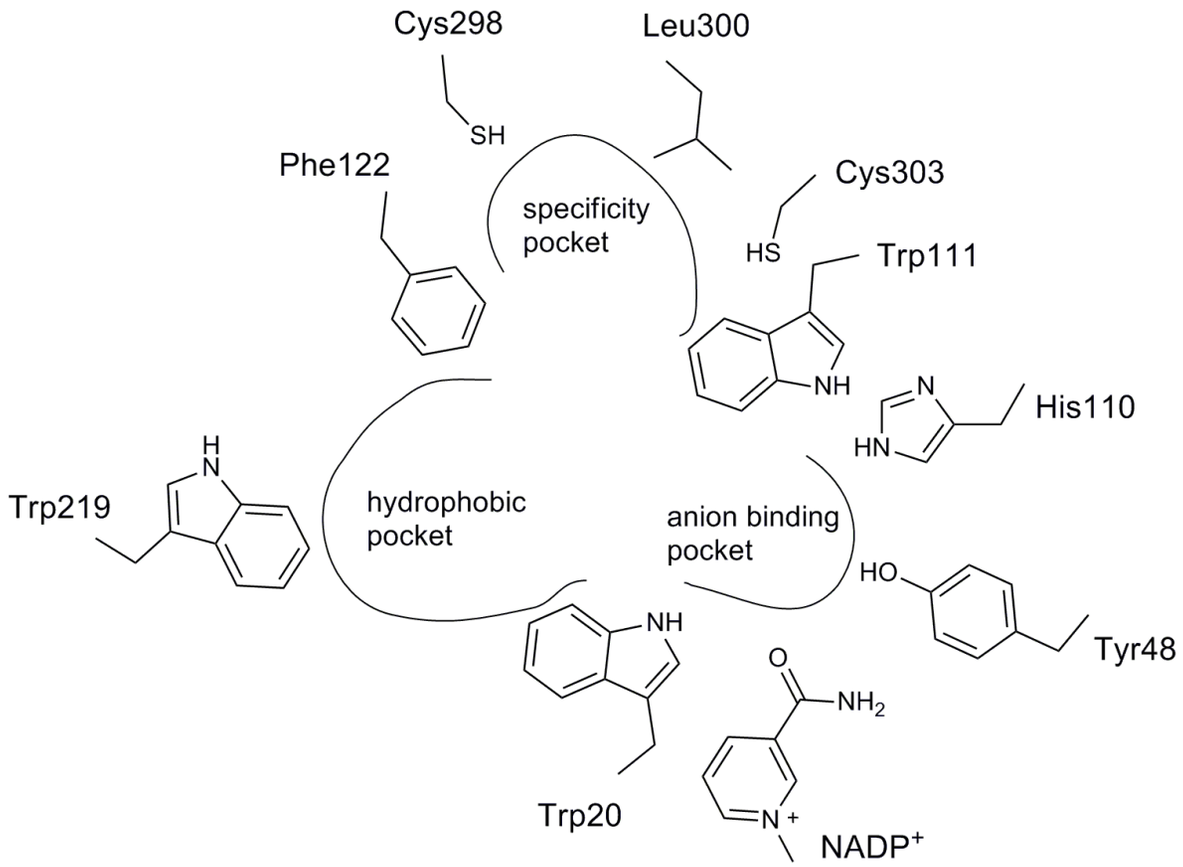


Figure 2. Proposed binding pockets in the active site of AR

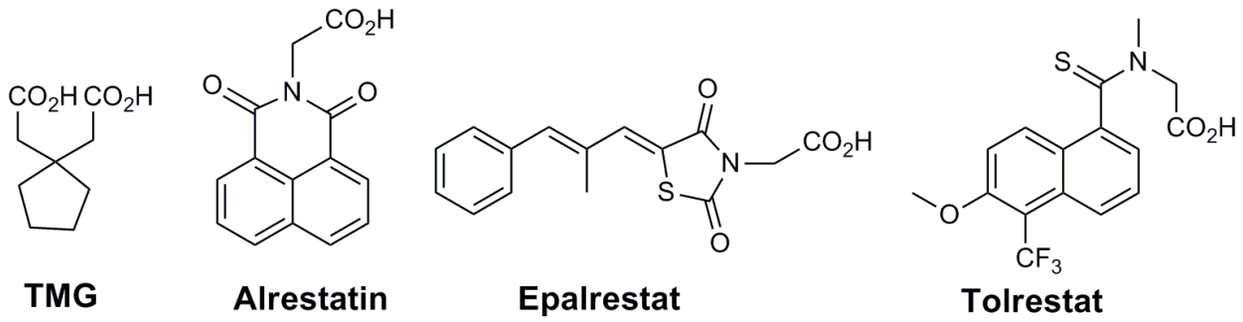
Aldehyde reductase (EC 1.1.1.2) , another member of the aldo-keto reductase superfamily, is mentioned here because of its close similarities to AR which may be associated with the specificity of ARIs. The two closely related enzymes share a high degree of sequence (~65%) and three dimensional structure homology with the majority of the differences present at the C-terminal end of the enzyme proteins, where is the region containing the least

conserved residues and lining the hydrophobic pocket of the active site called the specificity pocket [30, 39-42]. The specificity pocket is responsible for substrate and inhibitor specificity in the aldo-keto reductases.

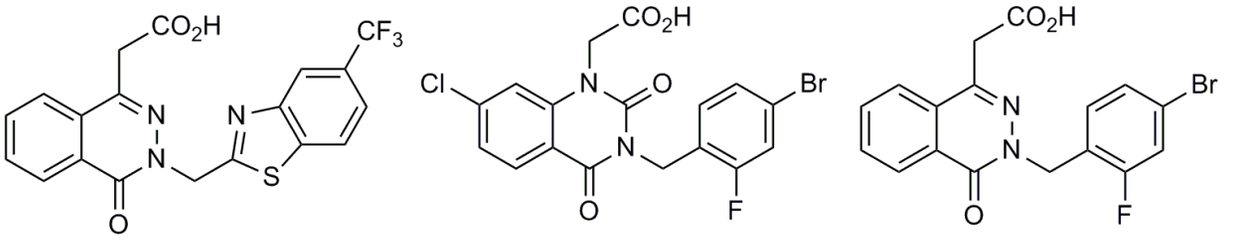
Aldehyde reductase plays a detoxification role, as it specifically metabolizes toxic aldehydes such as hydroxynonenal (HNE), 3-deoxyglucosone, and methylglyoxal, which arise in large quantities from pathological conditions connected with oxidative stress, as in hyperglycemia, and are intermediates for the formation of AGEs [43-45]. Thus, aldehyde reductase inhibition may account for some of the undesirable toxicities associated with the present ARIs. It is believable that the development of more structurally diverse ARIs and in turn the identification of molecularly targeted candidates that specifically block AR are important approaches in the search of new drugs.

3. AR inhibitors

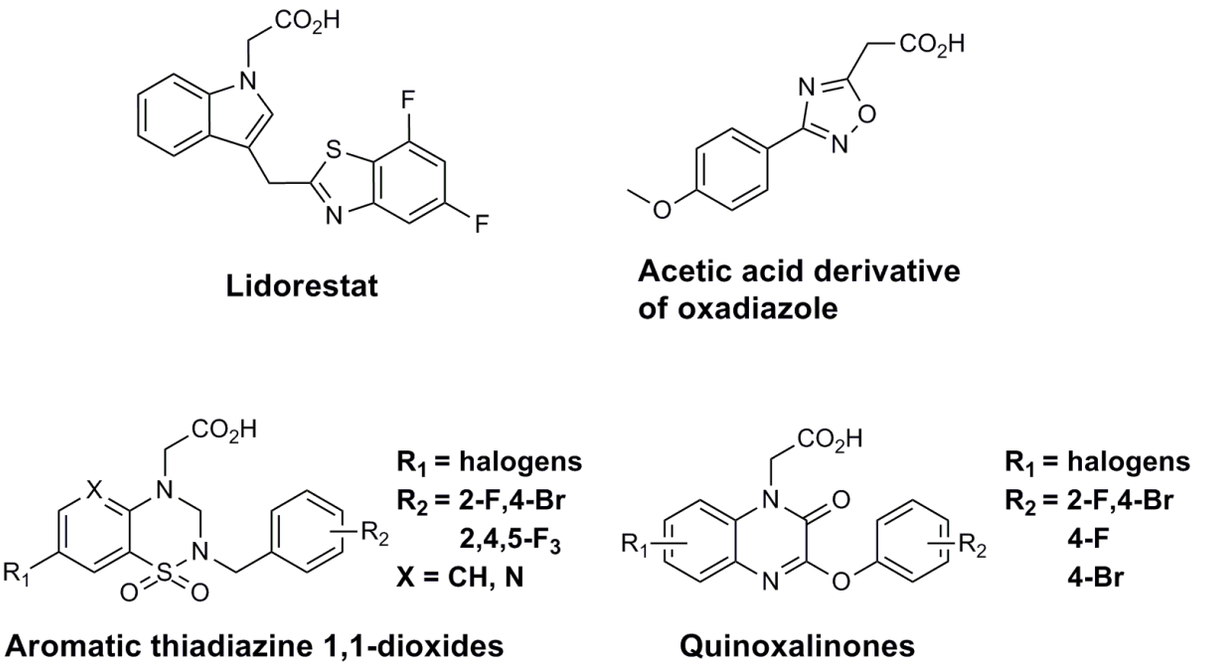
In spite of a range of structurally varied ARIs developed up to date [46, 47], carboxylic acids have been the most important and largest class of ARIs. This class readily shows activity in the AR inhibition because of the structural feature of carboxylate anion head group which may fit well in the so-called anion binding pocket of AR as described above (Figure. 2). At the beginning of research on AR properties, it was found that the enzyme is sensitive to organic anions, particularly to long-chain fatty acids [48], leading to the identification of tetramethyleneglutaric acid (TMG) as the first decent ARI in the 1960s. Since then, the more



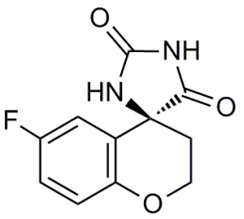
potent and early inhibitor alrestatin (AY-22,284) was developed [46]. Now the number of carboxylic acid ARIs is still growing. Among them is epalrestat, the only ARI given marketing approval as a therapeutic drug applied in the clinical treatment of diabetic neuropathy. Epalrestat was developed in 1983 [49] and has been marketed in Japan, and recently in China and India. Tolrestat, a strong ARI and potential drug for the treatment of diabetic complications [50], was approved to several markets, but withdrawn for the reason of risk of severe liver toxicity and death.The typical carboxylic acid ARIs also include zenarestat [51], zopolrestat [52], and ponalrestat [53]. Zenarestat is a potential drug for the treatment of diabetic neuropathy, retinopathy and cataracts. Both zenarestat and zopolrestat proceeded into late phase research of clinical trials. However, research results from Phase III trials showed zenarestat therapy in the dose level of 1200 mg/day to be linked with renal toxicity in a small number of patients [54]. Ponalrestat was withdrawn from clinical trials



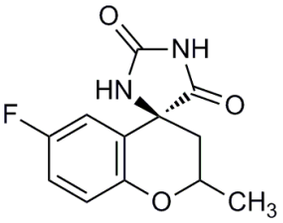
due to lack of efficacy. Besides, a number of potent ARIs were recently designed and synthesized based on various chemical core structures including (benzothiazol-2-yl)methyl-indole (lidorestat) [36], naphtho[1,2-d]isothiazole [55], oxadiazole [56], aromatic thiadiazine-1,1-dioxide [57, 58], and quinoxalinone [59]. All of them bear a chemical group of acetic acid on the core. However, poor tissue penetration has been observed as the major shortcoming for some individual inhibitors of the carboxylic acid ARI class [60, 61].



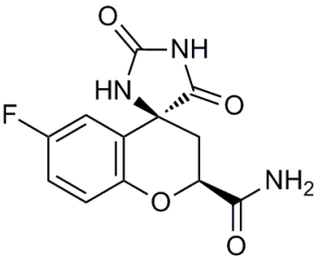
The second chemical class of ARIs includes spirohydantoin derivatives and their analogs. In this class, sorbinil was the first ARI capable of preventing the entire cataractogenic process in diabetic rats [62, 63]. The exquisite spiro system is well formed based on the combination of structures chroman and hydantoin. The hydantoin and the spiro in sorbinil may be key structures responsible for the strong inhibition against AR. In the binding interaction in the active site of AR, the hydantoin ring occupies the anion pocket as does the anion head group of carboxylate ARIs. Carbonyl oxygens and amino nitrogens in the hydantoin could make a



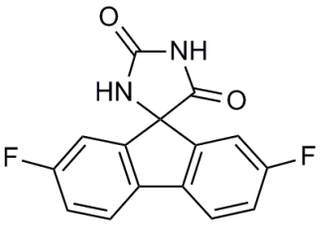
Sorbinil



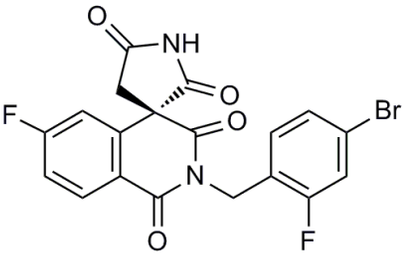
M79175



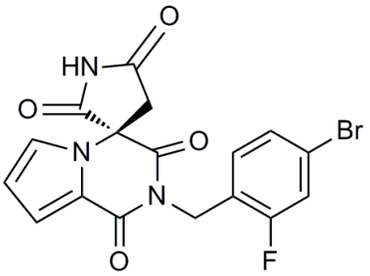
Fidarestat



Imirestat



Minalrestat

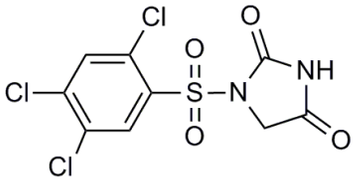


Ranirestat

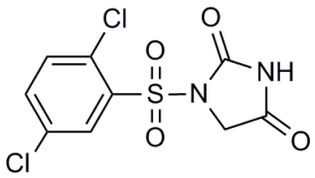
tight hydrogen-bonding network with residues Tyr48, His110 and Trp111 of AR [30]. The conformationally constrained spiro system made the ring planes of the hydantoin and chroman perpendicular to each other which may be the conformational shape of the inhibitor favored for the binding to AR. Sorbinil has proved an excellent ARI both in vitro and in vivo. However, in the research of clinical trials it was found that as many as 10% of patients receiving sorbinil may be at increased risk for developing hypersensitivity reactions characterized by fever, skin rash, and myalgia due to a potentially toxic intermediate oxidatively metabolized from sorbinil [64, 65]. The adverse reaction may also be attributed to the poor selectivity of sorbinil for AR versus aldehyde reductase [42].

While development of this important drug was hampered by potentially severe reactions, sorbinil has been a distinguish leading inhibitor or a reference widely used in the development of new ARIs and in the research of AR and the polyol pathway.

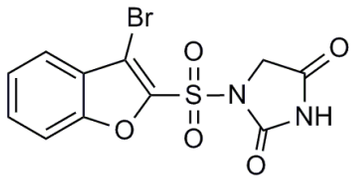
Based on the structure of sorbinil, several other spirohydantoins and related cyclic amides were developed. Addition of a methyl or a carbamoyl substituent at the 2-position of sorbinil resulted in the formation of M79175 and fidarestat, respectively. Replacement of the chroman ring system with a planar fluorene ring produced imirestat. Then, the spirohydantoin-like spiroimide minalrestat was formed by the replacements of both the chroman and hydantoin with isoquinoline-1,3(2H,4H)-dione ring and succinimide ring, respectively, and the addition of benzyl side chain at the 2-position. Further replacement of the isoquinoline-1,3(2H,4H)-dione ring of minalrestat with pyrrolo[1,2-a]pyrazine-1,3(2H,4H)-dione led to ranirestat (AS-3201) [66]. Imirestat was withdrawn from clinical trials due to toxicity. However, fidarestat and ranirestat have been identified as powerful ARIs with beneficial efficacy in diabetic complications [67-69]. There are no adverse effects reported to the two agents.



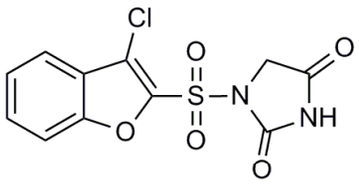
Tri-Cl-PSH



Di-Cl-PSH



M16209



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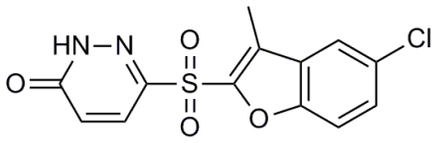
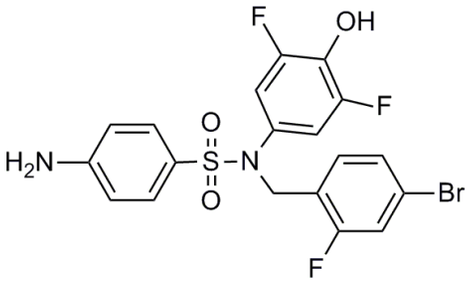
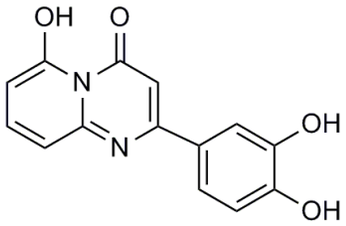


ARI-809



Benzenesulfonamide



ppp

In another design, the orthogonal spirohydantoin moiety of the above ARIs was changed into a more flexible structure, which is bridged by sulfonyl group leading to Tri-CI-PSH and Di-CI-PSH with IC_{50} values of 0.28 μM and 0.36 μM, respectively [70, 71]. They were found to inhibit sorbitol accumulation in the sciatic nerve completely and in the lens by up to 92%. Modification of aryl moieties of the arylsulfonylhydantoins has generated a group of benzofuransulfonylhydantoins. Of these, two compounds M16209 and M16287 indicated potent AR inhibition [72]. Recently, more modifications of the arylsulfonylhydantoins resulted in a new series of ARIs that are designed based on SO_2 linker-bearing sulfonylpyridazinone. Among them, the most potent and selective compound was profiled to be 6-(5-chloro-3-methylbenzofuran-2-sulfonyl)-2H-pyridazin-3-one (ARI-809) with IC_{50} value of 1 nM in vitro and ED_{50} of 0.8 mg/kg in vivo. ARI-809 is a highly selective (1:930) inhibitor of AR relative to aldehyde reductase, and such selectivity distinguishes it from sorbinil, which inhibits AR and aldehyde reductase to a comparable extent [73, 74]. In addition, introduction of phenol moiety into the sulfonyl-bridged system has provided benzenesulfonamide ARIs, which could not only inhibit AR but also exhibit potent antioxidant activity [75]. Moreover, phenylpyridopyrimidinone (PPP) was developed as a flavinoid bioisoster, and exhibited AR inhibition activity level in the submicromolar range and significant antioxidant properties [76].

4. Therapeutic properties of ARIs in the diabetic complications

The diabetic complications include typically neuropathy, nephropathy, and retinopathy and cataract although a substantial increase of atherosclerotic disease of large vessels, including cardiac and cerebral diseases, has been seen in the complications. ARIs appear to be a specific option for the improvement of the diabetic abnormalities according to the study results from experiments in vitro, in animal models, and clinical trials.

4.1. Retinopathy and cataract

Diabetic eye damages including retinopathy and cataract are characteristic of diabetes. ARIs sorbinil, ARI-809, ranirestat, fidarestat, zenarestat, M79175, and Kinostat™ have shown an activity for the treatment of the diabetic retinopathy and cataract. Kinostat™ is a new ARI developed by Kador [77].

It was found early that potent ARI sorbinil was effective in preventing cataractous changes in diabetic rats. Diabetic rats treated with sorbinil showed no lens changes during the 5-month period of the experiment. In contrast, untreated diabetic rats developed early lens changes by 3 weeks and dense nuclear opacities by 6 to 9 weeks [62]. It was evident by later independent studies in which sorbinil prevented the galactose-induced retinal microangiopathies and was also effective in preventing cataractous changes in diabetic rats [63]. In recent studies, treatment of diabetic Sprague Dawley rats with oral ARI imirestat prevented cataract by inhibiting sorbitol formation in the lens [78]. In insulinized streptozotocin-induced diabetic rats, ARI-809 improved survival, inhibited cataract development, normalized retinal sorbitol and fructose, and protected the retina from abnormalities that also occur in human diabetes: neuronal apoptosis, glial reactivity, and complement deposition [74]. Streptozotocin-diabetic rats could developed early lens opacities 8 weeks after streptozotocin injection and could have cataract. These alterations were prevented by the ranirestat treatment [69].

From several investigations performed recently with rat models, it appears that ARI fidarestat is active in the treatment of diabetic retinopathy. In streptozotocin-diabetic rats, fidarestat treatment reduced diabetes-associated cataract formation, and retinal oxidative-nitrosative stress, glial activation, and apoptosis [79]. Similar results were obtained in the rat model with retinal ischemia-reperfusion injury. The retinal injury-associated dramatic increase in cell death, elevated AR expression, and sorbitol pathway intermediate accumulation were prevented or alleviated by fidarestat treatment [80]. Also in the streptozotocin-diabetic rats, fidarestat treatment significantly decreased concentrations of sorbitol and fructose in the rat retinas. The expression of ICAM-1 mRNA and eukocyte accumulation in the retinas were significantly reduced. Immunohistochemical study also revealed the suppressive effect of fidarestat on the expression of ICAM-1 [81].

In addition, the study using Zucker diabetic fatty rats, an animal model of type 2 diabetes, showed that the administration of a combination of four plant extracts inhibited the development of diabetic cataract through the inhibition of AR activity and protein expression in diabetic lenses [82].

In galactose-fed dogs, cataract formation was delayed or prevented either by oral administration of the ARI M79175 [83, 84], or topical administration of the formulation Kinostat™ [77]. This has been further confirmed by the more recent experiment in a similar dog model. In a randomized, prospective, double-masked placebo control pilot study conducted with 40 dogs diagnosed with diabetes mellitus by topical administration of the ARI Kinostat™ for 12 months, the cataract score was significantly less with seven developing anterior equatorial vacuoles, two developing incipient anterior cortical cataracts, and four developing mature cataracts. It was noted that the cataract scores of the Kinostat™ group at 12 months did not in fact significantly increase from the score at the time of enrollment [85].

According to the results from phase III trial research in Japan, zenarestat developed as an eyedrop formulation was specifically effective for the treatment of diabetic retinopathy [54].

The beneficial effects of these different types of ARIs on the diabetic cataract and retinopathy support the notion that AR is the key relay that converts hyperglycemia into glucose toxicity in neural and glial cell types in the retina [74]. This provides a rationale for the development of ARIs, and in particular for the prevention and treatment of diabetic ocular complications [79].

4.2. Neuropathy

Nerve injuries of the respective organs are thought to be the root cause of diabetes complications. Pharmaceutical options in the treatment of diabetic neuropathy include antidepressants, anticonvulsants, tramadol, serotonin–norepinephrine reuptake inhibitors, and capsaicin [86]. These agents are modestly effective for symptomatic relief, but they do not affect the underlying pathology nor do they slow progression of the disease. In addition, they carry a risk of side effects. Therefore, the application of ARIs are expected to address this issue. Epalrestat, fidarestat, ranirestat (AS-3201), zenalrestat, sorbinil, and tolrestat will be described in this section.

4.2.1. Epalrestat

Epalrestat is undoubtedly the first agent for the treatment of diabetic neuropathy because of its effectiveness and safety. It is approved in Japan, China and India for the improvement of subjective neuropathy symptoms, abnormality of vibration sense and abnormal changes in heart beat associated with diabetic peripheral neuropathy. Long-term treatment with epalrestat in a clinic trial was well tolerated and could effectively delay the progression of diabetic neuropathy and ameliorate the associated symptoms of the disease, particularly in subjects with good glycemic control and limited microangiopathy [87]. Epalrestat is easily absorbed into neural tissue and potently inhibits AR with minimum adverse effects. Unlike the current pharmaceutical options for diabetic neuropathy, epalrestat may affect or delay progression of the underlying disease process. Data from experimental studies indicate that epalrestat reduces sorbitol accumulation in the sciatic nerve, erythrocytes, and ocular tissues in animals, and in erythrocytes in humans. On the bases of several clinical trials, treatment

with epalrestat in a dose of 50 mg 3 times/day may improve motor and sensory nerve conduction velocity and subjective neuropathy symptoms. The most frequently reported adverse effects for epalrestat include elevations in liver enzyme levels and gastrointestinal-related events such as nausea and vomiting [88].

The diabetic patients treated with epalrestat for 2 years showed a significant suppression of deterioration of motor nerve conduction velocity and minimum F-wave latency in the tibial nerve, and sensory nerve conduction velocity in the sural nerve. In fact, there was a significant difference in change in the level of serum N(ε)-carboxymethyl lysine after 1 year treatment. Therefore, it is suggested that epalrestat suppressed the deterioration of diabetic peripheral neuropathy, especially in the lower extremity, and the effects might be mediated by improvement of the polyol pathway and suppression of production of AGEs [89]. In a clinical trial in India, more than 2000 patients with diabetic neuropathy were treated with epalrestat for 3-12 months, the results showed that the improvement rate of the subjective symptoms was 75% and that of the nerve function tests 36%. Adverse drug reactions were encountered in 52 (2.5%) of the 2190 patients, none of which was severe [90]. Although data are limited, it is strongly suggested that epalrestat is a highly effective and safe agent for the treatment of diabetic neuropathy.

Clinical efficacy of epalrestat for diabetic peripheral neuropathy has been well documented by Hotta and coworkers [87, 91]. When patients with diabetic peripheral neuropathy were treated with epalrestat for period of 3 years, significantly better efficacy was found in patients with good glycaemic control and less severe diabetic complications. Nerve function deteriorated less or improved in patients whose symptoms improved. The odds ratio of the efficacy of epalrestat versus control subjects was approximately 2:1 [91].

In diabetic nerves, activation of the polyol pathway via AR and the resulting impairment of the Na(+)-K(+) pump would lead to a decreased transaxonal Na+ gradient, and thereby reduced nodal Na+ currents. In a 6-month, open clinical trial with epalrestat in 30 patients with mild-to-moderate diabetic neuropathy, results from excitability testing and extensive nerve conduction studies including F-wave analyses displayed that within a month of the start of treatment, there was a significant improvement in nerve conduction, particularly in conduction times across the carpal tunnel and F-wave latencies. It suggested an increased nodal persistent Na+ currents. At 6 months, nerve conduction continued to improve. Therefore, AR pathway inhibition could rapidly increase nodal Na+ currents and thereby improve the slowing of nerve conduction, presumably because of a restoration of the membranous Na+ gradient [92].

Earlier investigation on streptozotocin-induced diabetic neuropathy in rats showed that the treatment with epalrestat resulted in a significant improvement of nerve growth factor content and faster H-wave-related sensory nerve conduction velocity. At the same time, epalrestat treatment showed the stimulating effect on nerve growth factor synthesis/secretion in rat Schwann cell culture in vitro. Consequently, these results suggest that decreased levels of nerve growth factor in diabetic sciatic nerves may be involved in the pathogenesis of diabetic neuropathy in these rats and indicated that epalrestat can be useful

for the treatment of diabetic neuropathy through nerve growth factor-induction and inhibition of the polyol pathway [93].

Therefore, epalrestat may serve as a new therapeutic option to prevent or slow the progression of diabetic neuropathy. However, long-term, comparative studies in diverse patient populations are needed for clinical application.

4.2.2. Fidarestat

In a 52-week multicenter placebo-controlled double-blind parallel group study in 279 patients with diabetes and associated peripheral neuropathy, the group of fidarestat-treated at a daily dose of 1 mg was significantly improved compared with the placebo group in two electro physiological measures (i.e., median nerve F-wave conduction velocity and minimal latency). Subjective symptoms (including numbness, spontaneous pain, sensation of rigidity, paresthesia in the sole upon walking, heaviness in the foot, and hypesthesia) benefited from fidarestat treatment, and all were significantly improved in the treated versus placebo group. At the dose used, fidarestat was well tolerated, with an adverse event profile that did not significantly differ from that seen in the placebo group [94].

In experimental rats with diabetic neuropathy, oral administration of fidarestat at a dose of 1 or 4 mg/kg for 10 weeks significantly improved nerve blood flow, compound muscle action potential, and amplitude of C-potential. Fidarestat suppressed the increase in sorbitol and fructose, normalised reduced glutathione in sciatic nerve, and reduced the number of 8-hydroxy-2'-deoxyguanosine-positive cells in dorsal root ganglion neurons. This indicates that the fidarestat-improved neuropathy may be via an improvement in oxidative stress and supports a role for fidarestat in the treatment of diabetic neuropathy [95].

4.2.3. Ranirestat (AS-3201)

Ranirestat is an orally available ARI under development for the potential treatment of diabetic complications, such as neuropathy, cataracts, retinopathy and nephropathy [96]. It appears to be in late phase of clinical trials.

In the sciatic nerve and lens of streptozotocin-diabetic rats, ranirestat treatment reduced sorbitol accumulation in the sciatic nerve and improved the decrease in motor nerve conduction velocity. Morphological and morphometric examination of changes in sural nerve revealed that the treatment with ranirestat prevented both the deformity of myelinated fibers and the decrease in their axonal and myelin areas (atrophy). Ranirestat also averted the changes in the size frequency histogram of myelinated fibers. The studies showed that ranirestat is an agent for the management of diabetic sensorimotor polyneuropathy [69, 97].

Ranirestat has been well studied by Bril and coworkers [98, 99]. In a double-blind, placebo-controlled nerve biopsy trial study, 12-week-treatment with ranirestat at a dose of 5 or 20 mg/day improved nerve function in patients with diabetic sensorimotor polyneuropathy, and the improvement could be maintained. When patients completing this biopsy study

were offered a 48-week extension at the same ranirestat dose or at 5 mg/day ranirestat if they were originally treated with placebo, it was found that nerve conduction velocity of peroneal motor improved in the 20 mg/day group following 60 weeks of treatment while those of sural and median sensory improved after both 12 and 60 weeks of treatment with 20 mg/day. Vibration perception threshold improved after 60 weeks of treatment with 20 mg/day. The improved sensory nerve function observed after 12 weeks of therapy was maintained at 60 weeks, and improved motor nerve function was observed at 60 weeks. Ranirestat was found to be well tolerated with no difference in adverse events between the 5- and 20-mg/day groups [98]. In a further multicenter, double-blind study, patients with diabetic sensorimotor polyneuropathy were treated with 10, 20, or 40 mg/day ranirestat for 52 weeks. At week 52, the summed sensory (bilateral sural plus proximal median sensory) nerve conduction velocity did not show significant changes from baseline. However, significant improvement in the summed motor (peroneal, tibial, and median) nerve conduction velocity was observed with 20 and 40 mg/day ranirestat treatment at week 12 and at weeks 24 and 36. The peroneal motor nerve conduction velocity was improved at weeks 36 and 52 for the 20 mg/day ranirestat group. Therefore, the treatment with ranirestat might have an effect on motor nerve function in mild to moderate diabetic sensorimotor polyneuropathy. However, it failed to show a statistically significant difference in sensory nerve function relative to placebo. Ranirestat was well tolerated with no pertinent differences in drug-related adverse events or in effects on clinical laboratory parameters, vital signs, or electrocardiograms among the four groups [99].

4.2.4. Zenarestat

Zenarestat has proved to affect peripheral neuropathy in Zucker diabetic fatty rats, an animal model of type 2 diabetes. In the control group of Zucker diabetic fatty rats, a remarkable accumulation of sorbitol, a delay in F-wave minimal latency, and a slowing of motor nerve conduction velocity were observed compared with lean rat counterparts. Zenarestat, orally administrated at a dose of 3.2 mg/kg/day for 8 weeks, had no significant effect on the delay in F-wave minimal latency and the slowing of motor nerve conduction velocity, although the sorbitol accumulation in the sciatic nerve was partially inhibited. On the other hand, 32 mg/kg zenarestat treatment improved these nerve dysfunctions, along with a reduction of nerve sorbitol accumulation almost to the normal level [100]. Obviously, zenarestat could improve diabetic peripheral neuropathy in Zucker diabetic fatty rats. Also, the effects of zenarestat on nerves were confirmed in streptozotocin-induced diabetic rat model. When the diabetic model rats were maintained on a diet of containing 0.09% zenarestat for 8 weeks, endoneurial blood flow was significantly reduced by the application of nitric oxide synthase inhibitor, NG-nitro-L-arginine, whereas that in diabetic control rats was not affected by the inhibitor. Considerable levels of zenarestat were confirmed in the sciatic nerve in the drug treated rats. These thereby suggested that ARI zenarestat might restore or prevent the alteration of endoneurial blood flow resulting from an impairment of nitric oxide function [101]. The dorsal root ganglia has been identified as the target tissue in diabetic somatosensory neuropathy. Recent study in streptozotocin-induced diabetic rats

showed that the cell area of the dorsal root ganglia was smaller than that in normal rats, and a decrease in fiber size and a greater fiber density were apparent in the sural nerve. However, these morphological changes were reversed in diabetic rats treated with zenarestat. These functions of zenarestat in animal model also indicate that, in peripheral sensory diabetic neuropathy, hyperactivation of the polyol pathway may induce abnormalities not only in peripheral nerve fiber, but also in the dorsal root ganglia, which is an aggregate of primary sensory afferent cell bodies [102].

In an earlier study of randomized, placebo-controlled, double-blinded, multiple-dose, clinical trial, zenarestat was supplied for 52 weeks to patients with mild to moderate diabetic peripheral polyneuropathy. Dose-dependent increments in sural nerve zenarestat level and sorbitol suppression were observed along with significant improvement in nerve conduction velocity. Further analysis showed that zenalrestat doses producing >80% sorbitol suppression were associated with a significant increase in the density of small-diameter sural nerve myelinated fibers. Therefore, the slowing of nerve conduction velocity and the loss of small myelinated nerve fiber in diabetic peripheral polyneuropathy in humans could be improved by zenarestat treatment, but >80% suppression of nerve sorbitol content may be required [103].

In further studies of clinical trials, however, mixed results for effects of zenarestat on patiants were obtained. In a multicentered trial of zenarestat over 12 months, sural sensory velocity, median sensory amplitude, median distal motor latency, and cool thermal quantitative sensory testing declined significantly from baseline in the placebo group of patients [104]. After that, a larger size of multicenter trial of zenarestat treatment in 1100 patients was conducted but significant improvement could not be observed [105].

4.2.5. Sorbinil

Sorbinil has shown an effective approach for preventing peripheral nerve dysfunction and morphological abnormalities in nerves of diabetic animal models although it has the exact toxicity. Experimental diabetic neuropathy is characterized by sorbitol accumulation and myo-inositol depletion and usually also by enhanced turnover of particularly phosphatidylinositol-4,5-bisphosphate (PIP2). Nerves in the streptozotocin-diabetic rats exhibited 52% to 76% greater PIP2 labeling, markedly elevated sorbitol levels, and 30% less myo-inositol when compared with normal rats. In contrast, in nerves of diabetic rats that received the sorbinil-supplemented diet for either 4 or 8 weeks, both PIP2 labeling and myo-inositol levels were restored to normal [106]. Also in the streptozotocin-diabetic rats, the treatment with sorbinil at 65 mg/kg/day in the diet for 2 weeks resulted in complete inhibition of increased sorbitol pathway activity. The sorbinil-treatment improved diabetes-induced nerve functional changes; that is, decrease in endoneurial nutritive blood flow, motor and sensory nerve conduction velocities, and metabolic abnormalities including mitochondrial and cytosolic NAD+/NADH redox imbalances and energy deficiency. The treatment also restored nerve concentrations of two major non-enzymatic antioxidants, reduced glutathione and ascorbate, and completely arrested diabetes-induced lipid peroxidation [107].

Pressure-induced vasodilation, a neurovascular mechanism relying on the interaction between mechanosensitive C-fibers and vessels, allows skin blood flow to increase in response to locally nonnociceptive applied pressure that in turn may protect against pressure ulcers. In 8-week diabetic mice model, pressure-induced vasodilation, endothelial response, C-fiber threshold, and motor nerve conduction velocity were all altered in diabetic mice. The treatment with sorbinil for 2 weeks had a significant effect on motor nerve conduction velocity. Sorbinil restored acetylcholine-dependent vasodilation, C-fiber threshold, and pressure-induced vasodilation development. Therefore, sorbinil may improve vascular and C-fiber functions via the inhibition of AR and the polyol pathway [108].

Clinical investigations with sorbinil in patients with diabetic peripheral neuropathy showed an improvement both in motor and sensory nerve conduction velocities. Median nerve somatosensory evoked potential studies in patients showed significant sorbinil-related improvements in peripheral conduction and cortical responses. The incidence of sorbinil toxicity in 106 patients was 11.3 percent. Side effects were confined to rash, which was sometimes accompanied by fever, and disappeared rapidly after discontinuation of the drug [64].

4.2.6. Tolrestat

Tolrestat had proved to be an ARI with ability of treating diabetic complications, particularly nerve dysfunction although it was withdrawn because of its toxicity.

Patients with diabetic autonomic neuropathy have an increased cardiovascular mortality rate compared with diabetic patients without diabetic autonomic neuropathy. Heart rate variability time and frequency domain indices are strong predictors of malignant arrhythmias and sudden cardiac death. Treatment of the patients having diabetic autonomic neuropathy and diabetes mellitus by the administration of tolrestat at 200 mg/day for 12 months was evaluated in a randomised, double-blind, placebo-controlled trial. At the twelfth month, tolrestat, compared with placebo, had a beneficial effect on heart rate variability indices related to vagal tone. Heart rate variability indices remained less than that of patients with diabetes mellitus but without diabetic autonomic neuropathy, and healthy controls. The 12 patients of the 22 with moderate diabetic autonomic neuropathy benefited more than the 10 patients of the 22 with severe diabetic autonomic neuropathy. Moreover, no patient showed deterioration in heart rate variability indices with tolrestat as was seen with placebo [109]. Therefore, the effect of tolrestat on reduction in risk for malignant ventricular arrhythmias was suggested.

In an earlier study, the effects of tolrestat on chronic symptomatic diabetic sensorimotor neuropathy were evaluated during a placebo-controlled, randomised, 52-week multicenter trial. Of the four tolrestat doses investigated, only the highest dose group, 200 mg once daily, showed subjective and objective benefit over baseline and placebo. Significant improvements in both tibial and peroneal motor nerve conduction velocities were seen at 52 weeks. Tolrestat 200 mg once daily was significantly better than placebo in producing

concordant improvements in both motor nerve conduction velocities and paraesthetic symptom scores at 24 weeks. Benefit lasting for 52 weeks was seen in 28% of treated patients indicating some sustained improvement in symptomatic diabetic neuropathy [110].

4.3. Nephropathy

Increased flux through the polyol pathway is accompanied by the depletion of myo-inositol, a loss of Na/K ATPase activity, and the accumulation of sodium in diabetic nerves. Supportive evidence linking these biochemical changes to the loss of nerve function has come from studies in which ARIs block polyol pathway activity, prevent the depletion of myo-inositol and the accumulation of sodium, and preserve Na/K ATPase activity as well as nerve function. However, the pathophysiologic mechanisms underlying diabetic neuropathy may be different from those of diabetic nephropathy. In the kidney cortex in diabetic rats, polyol levels, medulla, and red blood cells were found to increase 2-9 folds, whereas myo-inositol levels decreased by 30% only in the kidney cortex and Na/K ATPase activity by 59% only in red blood cells. In contrast, in the rats treated with ARI tolrestat, only Na/K ATPase activity in red blood cells was improved although myo-inositol levels, Na/K ATPase, and conduction velocity in the sciatic nerve were preserved [111].

Thickening and reduplication of the tubular basement membrane has been suggested as an early event in diabetic nephropathy. During the incubation of confluent monolayers of LLC-PK1 cells grown on tissue culture, D-glucose treatment induced significant fibronectin accumulation in the basolateral compartment. The increase in fibronectin concentration in response to glucose was inhibited by sorbinil [112]. Moreover, glucose activation of the polyol pathway may lead to renal arteriolar smooth muscle and glomerular mesangial cell hypocontractility. In the streptozotocin-induced diabetic rats, functional alterations including increase in glomerular filtration rate, raised glomerular permeability to albumin, and glomerular hypertrophy were prevented by administration of tolrestat. Endothelin-1-induced contraction of isolated glomeruli was normal in tolrestat-treated diabetic animals compared with the hypocontractile diabetic glomeruli. Fractional mesangial expansion was unchanged in tolrestat-treated diabetic rats compared with untreated animals [113].

Both increased AR activity and oxidative/nitrosative stress have been implicated in the pathogenesis of diabetic nephropathy. In vitro studies revealed that accumulation of nitrosylated and poly(ADP-ribosyl)ated proteins in cultured human mesangial cells was induced by D-glucose but stopped by L-glucose or D-glucose plus fidarestat. In animal experiments, concentrations of sorbitol and fructose were significantly increased in the renal cortex of streptozotocin-diabetic rats and then prevented by fidarestat-treatment. Fidarestat at least partially prevented diabetes-induced increase in kidney weight as well as nitrotyrosine (a marker of peroxynitrite-induced injury and nitrosative stress), and poly(ADP-ribose) (a marker of polymerase activation) accumulation in glomerular and tubular compartments of the renal cortex. These results indicate that fidarestat treatment counteracts nitrosative stress and polymerase activation in the diabetic renal cortex and high-glucose-exposed human mesangial cells [24].

Long-term clinical trial study has shown beneficial effect of epalrestat on the development of incipient diabetic nephropathy in type 2 diabetic patients. At the end of the study conducted for 5 years, urinary albumin excretion increased significantly in the control group whereas it remained unchanged in the epalrestat-treated group. However, the reduction rate of reciprocal creatinine in the epalrestat-treated group was significantly smaller than that in the control group [114].

4.4. Others

As described in the preceding section of this chapter, the increased flux of the polyol pathway by hyperglycemia is implicated in the pathogenesis of diabetic complications, and one of the linkages has been proposed to be an increase in oxidative stress mediated by ROS. Early, it was found that some of enzymes responsible for oxidative defense were altered by treatment of ARI imirestat, particularly in rabbit livers, although direct changes in lipid peroxidation within normal rat and rabbit livers were not detected [115]. Clinical trial study in patients with type 2 diabetes mellitus revealed that administration of epalrestat at 150 mg/day for 3 months prevented adverse alterations in the levels of oxidative stress markers and antioxidants including plasma thiobarbituric acid-reactive substances, malondialdehyde-modified low-density lipoprotein, and vitamin E or β-carotene. In addition, epalrestat significantly reduced lipid hydroperoxides in erythrocytes [116]. The role of ARIs in the reduction of oxidative stress associated with diabetic complications is receiving increasing attention.

Very recently, Srivastava and co-workers found that alcohols, products from the reduction of ROS-induced lipid peroxidation-derived lipid aldehydes such as 4-hydroxy-trans-2-nonenal (HNE) and their glutathione-conjugates, are generated by AR catalysis and mediate inflammatory signals. Therefore, ARI fidarestat significantly prevented tumor necrosis factor-alpha (TNF-α)-, growth factors-, lipopolysachharide (LPS)-, and environmental allergens-induced inflammatory signals that cause various inflammatory diseases. Moreover, inhibition of AR significantly prevented the inflammatory signals induced by cytokines, NF-kappa B, growth factors, endotoxins, high glucose, allergens, and auto-immune reactions in cellular as well as animal models. Also, it significantly ameliorated the diseases in animal models of inflammatory diseases such as diabetes, cardiovascular, uveitis, asthma, and cancer (colon, breast, prostate and lung) and metastasis. Thereby ROS-induced inflammatory response could be reduced with ARIs [117, 118].

On the other hand, beneficial effects of ARI zopolrestat at 500 or 1,000 mg/day for 1 year on asymptomatic cardiac abnormalities were identified in patients with diabetic neuropathy in a double-blind placebo-controlled clinical trial study. In the zopolrestat treatment group, there were significant increases in resting left ventricular ejection fraction, cardiac output, left ventricular stroke volume, and exercise left ventricular ejection fraction. The increase in exercise left ventricular ejection fraction was independent of blood pressure, insulin use, or the presence of baseline abnormal heart rate variability. In contrast, there were decreases in exercise cardiac output, stroke volume, and end diastolic volume in the control group [119].

Furthermore, the beneficial effects of AR inhibition has been shown on the esophageal dysfunction in diabetic patients. When type 2 diabetic patients with peripheral neuropathy were administered with the ARI epalrestat at 150 mg/day for 90 days, parameters related to the gastroesophageal acid reflux and the esophageal motility were remarkably improved. These parameters include % time of pH<4, DeMeester score, duration of the longest reflux episode, reflux episodes longer than 5 min, ratios of peristaltic waves with the amplitude greater than 25 mmHg, and ratios of effective peristalsis [120].

5. Summary and perspective

The increased activities of AR and the consequent polyol pathway are believed likely to be the mechanism of diabetic complications. They have been shown to be involved in the diabetic alterations including particularly diabetic neuropathy, nephropathy, retinopathy, and cataract. The relevance of AR inhibition to the improvements of diabetic changes suggests the design of drugs that specifically target the polyol pathway, particularly AR, the rate-limiting enzyme of the pathway. There has been a considerable effort to develop small molecules useful for the AR inhibition over the past decades and a number of potent ARIs have been identified. These ARIs have proven effective in studies in vitro and some of them have been advanced to late phases of clinical trials. In particular, epalrestat has been marked in Japan for years and recently approved to markets in China and India.

While AR and the polyol pathway are promising targets for the treatment of diabetic complications and pharmaceutical developments, some ARIs able to redress all aspects of the polyol pathway but they in vivo or in clinical trials give a poor or only a partial amelioration, and some show unacceptable toxicities. For example, a long-term AR inhibition in diabetic dogs prevented sorbitol accumulation in erythrocytes and even diabetic neuropathy, but showed no beneficial effect on renal structure or albuminuria. It failed to prevent retinopathy or thickening of the capillary basement membrane in the retina, kidney and muscle [121, 122]. The similar results were observed in a transgenic rat model with human AR cDNA. In this model, AR inhibition was without effect on microalbuminuria, which follows glomerular and tubular dysfunction [123]. Fidarestat seems clinically not very effective, although it has already undergone late phase clinical trial for diabetic neuropathy and found to be safe [117]. As a result, very few ARIs could be passed through late stage of clinical trials, and only epalrestat is on the markets.

Several reasons may be suggested for these inconsistent and adverse effects with ARIs or AR inhibition. First, knowledge of structure and particularly conformational shape of AR active site has yet to be sufficiently acquired for the discovery of more specific ARIs. Amino acid sequences of AR were suggested to have a relatively low sequence identity conserved among human, rat, and other animal species although the existence of tissue-specific isoforms for human AR has not been verified [124]. This could account for the species-dependent differences in the sensitivity of AR to some of the inhibitors. Moreover, the conformational shape of AR active center may be variable depending on animals and tissues, and accurate conformation remains to be identified. Second, the diverse

complications may not share the same mechanisms. At least evidence for a uniform pathogenetic mechanism is far from established although a single unifiying mechanism for diabetic complications was suggested [23] and the polyol pathway has proved to be the most attractive.

Therefore, further studies regarding the structural features of AR and identification of more specific ARIs are of importance to the understanding of the mechanism of diabetic complications and the treatment of the diseases.

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6. References

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