Journal of Molecular and Genetic Medicine

Sango et al., J Mol Genet Med 2014, S1:012
DOI: 10.4172/1747-0862.S1-012

Mini Review Open Access

Physiological and Pathological Roles of Aldose Reductase in Schwann Cells

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Received date: December 17, 2013; **Accepted date:** January 20, 2014; **Published date:** January 27, 2014

Abstract

Aldose reductase (AR), the first enzyme in the polyol pathway, is predominantly localized to Schwann cells in the peripheral nervous system (PNS). The exaggerated glucose flux into the pathway via AR in Schwann cells under diabetic conditions is thought to be a major contributing factor in the pathogenesis of diabetic neuropathy, and the restoring effects of AR inhibitors on the neurological symptoms of experimental diabetic animals and patients with diabetes have been investigated. In contrast, however, much less attention has been paid to the physiological functions of AR in the PNS and other tissues (i.e. osmoregulation, aldehyde detoxification, and steroid and catecholamine metabolism). In this paper, we focus on the functional significance of AR in Schwann cells under normal and diabetic conditions. A spontaneously immortalized adult mouse Schwann cell line IMS32 displays distinct Schwann cell phenotypes and high glucose (30 mM)-induced upregulation of AR expression and accumulation of sorbitol and fructose. This cell line can be a useful model to study the physiological and pathological roles of AR in the PNS, especially the interactions between the polyol pathway and other pathogenetic factors of diabetic neuropathy, and the functional redundancy of AR and other enzymes in aldehyde detoxification.

Keywords: Diabetic neuropathy; Aldose reductase; Polyol pathway; Schwann cells; Toxic aldehydes

Introduction

Diabetic neuropathy, one of the most common and intractable complications of diabetes mellitus, is characterized by progressive, nerve length-dependent loss of peripheral nerve fibers, causing decreased sensation, spontaneous pain, autonomic dysfunction, and eventually complete loss of sensation [1]. Although its pathogenesis remains unclear, metabolic disorders due to insulin deficiency and hyperglycemia appear to be closely related to its development and progression. Chronic hyperglycemia increases the flux of the polyol and hexosamine pathways, accelerates the formation of advanced glycation end-products (AGEs), alters the protein kinase C activity, enhances oxidative stress, and impairs synthesis and axoplasmic transport of neurotrophic factors [2,3]. Vascular factors such as decreased nerve blood flow and increased aggregation are also considered important in the pathogenesis [4,5]. Recent studies have implicated cross talks among these glucose-mediated metabolic and vascular abnormalities [6]. As glial cells in the peripheral nervous system (PNS), Schwann cells are responsible for providing trophic support for the growth and maintenance of neurons and ensheathing their axons in either a myelinating or an unmyelinating form during development and regeneration [7]. Schwann cell abnormalities as a result of the hyperglycemia-related metabolic and vascular disorders can be a cause of reduced nerve conduction velocity (NCV), axonal atrophy, and impaired axonal regeneration [8]. In addition, recent experimental and clinical studies suggest that dyslipidemia due to obesity and type 2 diabetes may play a role in the development and progression of peripheral neuropathy. For instance, impaired lipid and cholesterol metabolism in Schwann cells under diabetic conditions may affect the structure and function of peripheral myelins [9,10].

The role of Schwann cells in diabetic neuropathy is often discussed in relation to the polyol pathway hyperactivity. Aldose reductase (AR: EC 1.1.1.21), the first enzyme in the polyol pathway, is predominantly localized to Schwann cells in the PNS [11]. The increased glucose flux into the pathway via AR and the subsequent accumulation of sorbitol in Schwann cells can directly or indirectly affect peripheral nerve functions. Transgenic mice expressing human AR in Schwann cells under the control of the rat myelin protein zero (P0) promoter displayed more severe neuropathy (e.g. decreased NCV and GSH level, and myelinated fiber atrophy) than non-transgenic littermates under diabetic conditions [12]. In contrast, AR-deficient mice were protected from the diabetes-induced reduction of NCV and GSH, and sural nerve fiber loss [13]. These findings indicate that increased polyol pathway flux through AR is a major contributing factor in the pathogenesis of diabetic neuropathy, and the benefits of AR inhibition in the neuropathy and other complications have been extensively studied on experimental diabetic animals and patients with diabetes [14-16]. Among numerous AR inhibitors, epalrestat is currently available for clinical use in Japan [17]. In contrast, however, the physiological functions of AR under normoglycemic conditions (i.e. osmoregulation, aldehyde detoxification, and steroid and catecholamine metabolism) [18] have been neglected or underestimated. In this paper, we focus on the functional significance of AR in the PNS, especially Schwann cells, under normal and diabetic conditions.

AR in Glucose Toxicity

Under hyperglycemic conditions, the acceleration of the polyol pathway induces various metabolic changes in tissues that undergo insulin-independent uptake of glucose, namely the 'target' organs of diabetic complications (e.g. ocular lens, retina, peripheral nerve, and renal glomerulus). The polyol pathway is a two-step metabolic pathway in which glucose is reduced to sorbitol, which is then oxidized to fructose. In the first and rate-limiting step of this pathway, glucose is metabolized to sorbitol by reduced nicotinamide adenine dinucleotide phosphate (NADPH)-dependent AR. In the second step, sorbitol is converted to fructose by nicotinamide adenine dinucleotide (NAD+)-dependent sorbitol dehydrogenase (SDH: EC 1.1.1.14). Under normoglycemia, most of the cellular glucose is phosphorylated into glucose 6-phosphate by hexokinase and enters the glycolytic pathway, and less than 3% of the glucose enters the polyol pathway (Figure 1). Under hyperglycemia, however, 30–35% of the glucose can be converted to sorbitol as a result of the saturation of the glycolytic pathway and the subsequent escalation of the glucose flux into the polyol pathway [18] (Figure 2). It has been proposed that the increase in AR activity in Schwann cells under hyperglycemic conditions affects nerve functions through various mechanisms:

1) Sorbitol accumulation leads to osmotic stress and the depletion of myo-inositol and taurine [19,20]. Because myo-inositol is an important constituent of the phospholipids that make up neural cell membranes, its depletion causes a decrease in phosphoinositide and diacylglycerol levels, with subsequent decreases in Na^+–K^+-ATPase activity and NCV [21,22]. Taurine is a sulfur-containing free amino acid and has multiple roles as an antioxidant, osmolyte, calcium modulator and neurotransmitter. Taurine depletion appears to increase oxidative and nitrosative stress in Schwann cells [23].

2) The increase in AR activity competes with nitric oxide (NO) synthase or glutathione reductase for NADPH. The inhibition of NO synthase and the subsequent decrease in NO in the nervous tissue causes diminished nerve blood flow, whereas the depletion of reduced glutathione (GSH) by glutathione reductase inhibition results in the excessive production of free radicals and the enhancement of oxidative stress [24,25].

3) Sorbitol is converted to fructose by SDH; fructose and its metabolites, such as fructose-6-phosphate and triose-phosphate, can be triggers of glycation and oxidative stress [26].

It seems reasonable to suppose that the amount of glucose available for utilization through the polyol pathway under normoglycemic conditions is insufficient to cause sorbitol accumulation even though AR expression is increased. However, in addition to hyperglycemic insults, ischemia-reperfusion injury and hyperosmotic stress have been shown to enhance the activity of AR and the glucose flux into the polyol pathway [27,28]. The precise mechanisms for the acceleration of glucose uptake and/or utilization as a substrate for AR under those non-diabetic conditions remain unclear.

Physiological Roles of AR

As compared with a considerable number of studies on AR in glucose toxicity, much less attention has been paid to the functional significance of AR under normoglycemic conditions. AR is a member of the aldo-keto reductase (AKR) superfamily [29], and reduces a variety of aldehydic substrates in an NADPH-dependent manner (Figure 3).

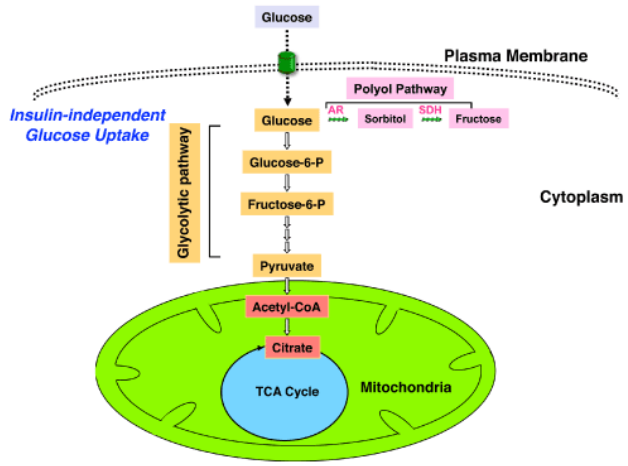

Figure 1: Shematic representation of glucose metabolism in Schwann cells under a normoglycemic condition, Most of the cellular glucose enters the glycolytic pathway, and less than 3% of the glucose enters the polyol pathway.

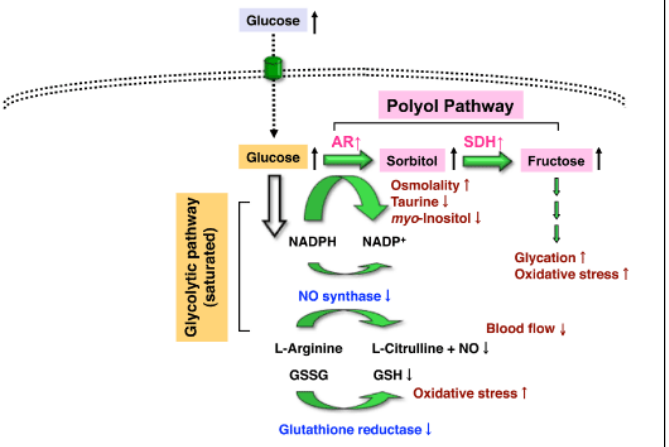

Figure 2: Shematic representation of glucose metabolism in Schwann cells under a hyperglycemic condition. As a result of the saturation of the glycolytic pathway and the increase in AR activity, 30–35% of the cellular glucose enters the polyol pathway and can be converted to sorbitol and fructose. The polyol pathway-related metabolic disorders are described in the text.

Osmoregulation and fructose production via polyol pathway

Through the polyol pathway, AR plays a role in osmoregulation in the kidney and fructose production in the male genital tract [18]. In the latter, fructose converted from sorbitol by SDH is an energy source of sperm cells [30]. Even in the absence of hyperglycemia, hyperosmotic stress is known to cause AR activation and sorbitol accumulation in renal papillary interstitial cells [31]. Because sorbitol is one of the organic osmolytes that balance the osmotic pressure of extracellular sodium chloride (NaCl), AR appears to be a key enzyme in the renal osmoregulation [32]. This idea is supported by the fact that AR-deficient mice display defective urine-concentrating ability

[13]. In addition to the renal cells, hyperosmotic stress has been shown to increase the AR expression and/or sorbitol contents in a variety of cells, including Schwann cells [33,34]. However, the functional significance of AR as an osmoregulatory factor in these cells remains unclear.

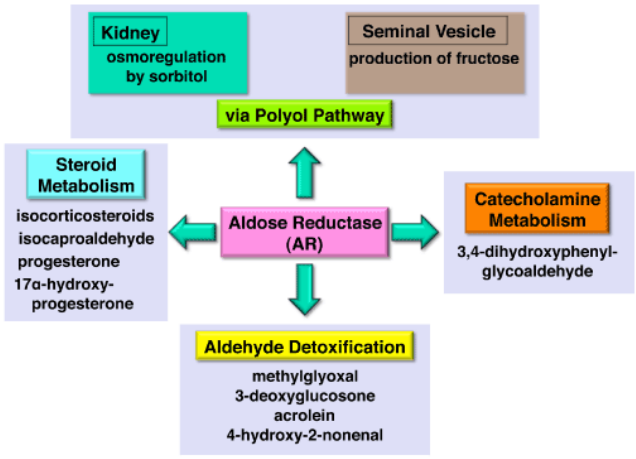

Figure 3: A diversity of substrates and putative physiological roles of AR [18].

Aldehyde reduction

AR and other aldo-ketoreductases catalyze the reduction of reactive biogenic aldehydes, such as methyglyoxal (MG), 3-deoxyglucosone (3-DG), acrolein and 4-hydroxy-2-nonenal (4HNE) [18]. Treatment with AR inhibitors augmented the cytotoxic effects of reactive aldehydes in cultured smooth muscle cells [35] and lens epithelial cells [36]. These findings provide evidence to support the protective role of AR against the cytotoxic aldehydes in normoglycemic conditions. On the other hand, a lack of apparent phenotypes except slightly defective urine-concentrating ability in AR-deficient mice [13] led us to speculate that the detoxification function may be taken over by other enzymes (e.g. aldehyde reductase (AHR), aldehyde dehydrogenase (ALDH), and glutathione-dependent glyoxalase system) in the absence of AR [37,38]. A recent study suggests the ability of various AKR enzymes (e.g. AKR1B, AKR1C and AKR7A) to protect human neuroblastoma cells against the aldehyde toxicity [39].

AR catalyzes the reduction of lipid aldehydes and their glutathione (GSH) conjugates generated during lipid peroxidation [40] (Figure 4), but these reactions do not necessarily mean detoxification. Rather, the reduced GS-aldehydes may trigger inflammatory reactions via activating transcription factors, such as NF-κB and AP-1 [41]. Growing evidence that AR inhibition-dependent NF-κB inactivation negatively regulates the transcription and expression of various inflammatory genes suggests a possible efficacy of AR inhibitors for the treatment of inflammatory diseases (e.g. atherosclerosis, sepsis, asthma, uveitis, colon cancer, and neuroinflammatory diseases) [41,42]. However, this hypothesis is still controversial and the mechanisms for the detoxification of the GS-aldehydes in the presence or absence of AR remain to be solved. Contrary to this hypothesis, Keith et al. [43] observed that endoplasmic reticulum (ER) stress induced by aldehydic products of lipid peroxidation after ischemia-reperfusion injury was diminished in the hearts of cardiomyocyte-specific transgenic mice overexpressing the AR transgene.

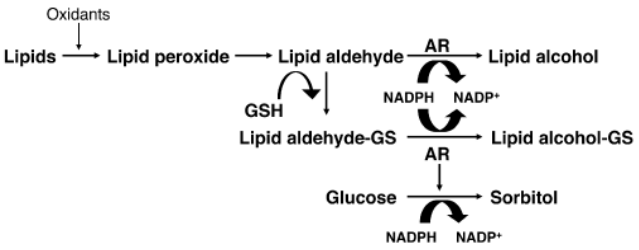

Figure 4: Involvement of AR in the reduction of lipid aldehydes and their glutathione (GSH) conjugates generated during lipid peroxidation [40].

Steroid and catecholamine metabolism

AR and AHR catalyze the reduction of biogenic aldehydes derived from the catabolism of the steroid hormones, catecholamines and serotonin. In the steroid metabolism, isocorticosteroids and isocaproaldehyde are the preferred substrates for AR. Isocaproaldehyde, produced in large amount in the adrenal cortex during steroidgenesis, displays cytotoxic actions *in vitro*, and AR can be a detoxifying enzyme in this tissue [44].

Dopamine is deaminated to 3,4-dihydroxyphenylacetaldehyde (DOPAL) by monoamine oxidase (MAO). This aldehyde is highly unstable, and mostly oxidized to 3,4-dihydroxyphenylacetic acid (DOPAC) by ALDH and partially reduced to 3,4-dihydroxyphenylethanol (DOPET) by AR or AHR [45]. Similarly, norepinephrine is deaminated to 3,4-dihydroxymandelaldehyde (DHMAL) by MAO and subsequently converted to either 3,4-dihydroxymandelic acid (DHMA) by ALDH or 3,4-dihydroxyphenylglycol (DHPG) by AR or AHR. In rat sympathetic neurons, AR appears to be a predominant enzyme to catalyze the formation of DHPG, but AHR can compensate for this reaction when AR is inhibited [46].

AR in Cultured Schwann Cells Under Normal and Diabetic Conditions

Culture systems of Schwann cells appear to be useful for precise investigation of polyol pathway hyperactivity and other metabolic changes under diabetic conditions [47]. A cell line from rat Schwannoma, JS1 [33], and primary cultured adult rat Schwann cells [48] have been introduced to study polyol metabolism. However, these cells did not display intracellular sorbitol accumulation or enhanced AR expression under high glucose (25–30 mM) conditions, unless hyperosmotic stress (greater than 100 mM) was applied.

We have established spontaneously immortalized Schwann cell lines from adult ICR mice. One of the cell lines, IMS32, displays distinct Schwann cell phenotypes such as a spindle-shaped morphology and the expression of glial cell markers [e.g. S100, glial fibrillary acidic protein (GFAP), p75 low-affinity neurotrophin receptor (p75NTR)], transcription factors [e.g. PAX3, Krox20, Oct6, Sox10], myelin proteins [e.g. P0, peripheral myelin protein 22 kDa (PMP22)] and neurotrophic factors [e.g. nerve growth factor (NGF), glial cell line-derived neurotrophic factor (GDNF), ciliary

neurotrophic factor (CNTF)] [49,50]. Conditioned medium obtained from IMS32 cells enhanced the neurite elongation of PC12 rat pheochromocytoma cells, suggesting that IMS32 cells secrete various neurotrophic factors and cytokines that promote axonal regeneration. However, we failed to demonstrate that the cell line could myelinate neurites in the same manner as endogenous Schwann cells in the peripheral nerves and primary cultured Schwann cells. The high proliferative activity of IMS32 cells may impede continuous and stable neuron-Schwann cell interactions, which usually take 4 weeks or longer to form the myelin sheath. IMS32 cells appear to be one of the best-characterized Schwann cell lines at present, and we observed increased AR mRNA / protein expression and marked accumulation of sorbitol and fructose in IMS32 cells cultured under a high glucose (30 mM) condition. Further, application of an AR inhibitor, fidarestat (Sanwa Kagaku Kenkyusho, Nagoya, Japan), to the high glucose medium diminished the intracellular sorbitol content to a level close to a normal (5.6 mM) glucose medium [34]. Taking these findings into consideration, the culture of IMS32 under high glucose conditions can be a suitable *in vitro* model for the study of polyol pathway-related abnormalities in diabetes.

In addition to IMS32, we have recently established an immortalized Schwann cell line IFRS1 from adult Fischer 344 rats. IFRS1 cells retain the characteristic features of Schwann cells as described above and the fundamental ability to myelinateneurites in coculture with adult rat dorsal root ganglion (DRG) neurons and NGF-primed PC12 cells [51,52]. Unlike IMS32 cells, however, neither AR expression nor intracellular polyol levels were enhanced by exposure of IFRS1 cells to a high glucose (30 mM) condition (Tsukamoto et al. unpublished data). This finding is in sharp contrast to the much higher AR expression in the nervous tissue of rats than that of mice [53], and it remains to be elucidated why an increase in the glucose concentration accelerated the polyol pathway in IMS32, but not in primary cultured rat Schwann cells or IFRS1 cells. In contrast to the rapid proliferation of IMS32 cells even in the absence of exogenous growth stimulants, neuregulin-β and forskolin are needed for the growth and passage of IFRS1 cells. The lower proliferative activity of IFRS1 cells than IMS32 cells is advantageous for myelin formation in coculture with neuronal cells, because overgrowth of IFRS1 cells can be prevented during the coculture. On the other hand, the lower proliferative activity of IFRS1 cells might be, at least partly, attributed to its much lower capacity to store sorbitol and other glucose-derived metabolites than IMS32 cells.

The activated AR enhances the flux through the polyol pathway by converting glucose to sorbitol, but it may also act against reactive aldehydes and related substances produced by lipid peroxidation and oxidative stress in Schwann cells under hyperglycemic conditions. We observed that reduced mRNA expression of AHR in IMS32 cells under the high glucose condition was completely ameliorated by treatment with fidarestat [34]. Both AR and AHR appear to be able to neutralize lipid peroxidation products [54], but AHR is virtually inactive for glucose and other aldo-sugars [55]. Our study suggests that the production of AHR is suppressed by augmented expression and activity of AR in Schwann cells during hyperglycemic conditions. Conversely, AR inhibition may up-regulate AHR to be more active against the toxic substances induced by high glucose. This idea is partly supported by previous studies suggesting the functional redundancy of the two enzymes in rat sympathetic ganglia, as described above [46,56].

Conclusion

We can safely state that the activation of AR and subsequent acceleration of the glucose flux into the polyol pathway in Schwann cells play a key role in the development and progression of diabetic neuropathy. However, the efficacy of AR inhibition for the restoration of the neuropathy is not entirely satisfactory, and physiological and pathological roles of AR in the reduction of biogenic aldehydes in Schwann cells need further consideration. We have recently established a spontaneously immortalized Schwann cell line from AR-deficient mice (Tsukamoto et al. in preparation). By employing this cell line, we would now like to elucidate the interactions between the polyol pathway hyperactivity and other pathogenetic factors of diabetic neuropathy, and the functional redundancy of AR and other enzymes in aldehyde detoxification under diabetic and non-diabetic conditions.

Acknowledgements

Our work reported in this review was supported by Grants-in-aid for Scientific Research from the Ministry of Education, Science, Sports and Culture of Japan (grant number: 22500324 and 25430056). We thank Drs. Soroku Yagihashi, Hitoshi Yasuda, Chihiro Yabe-Nishimura, Sookja K. Chung and Hiroki Mizukami for helpful suggestions, and Emiko Kawakami, Shizuka Takaku, Hiroko Yanagisawa, Kentaro Endo, and the late Kyoko Ajiki for technical assistance.

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This article was originally published in a special issue, entitled: **"Molecular & Cellular Aspects in Obesity and Diabetes"**, Edited by Dr. Masayoshi Yamaguchi, Emory University School of Medicine, USA