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Review

D-ribose in glycation and protein aggregation

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ABSTRACT

Background: D-ribose is a naturally occurring pentose monosaccharide present in all living cells and their microenvironments and is a key component of numerous biomolecules involved in many important metabolic pathways. It also participates in the glycation of proteins producing advanced glycation end products (AGEs) that lead to cell dysfunction and death. As recent studies show, ribosylation, a rapid process, causes protein aggregation in vitro and in vivo.
Scope of review: This review summarizes the relationship between ribosylation, protein aggregation, cell death and cognitive impairments.
Major conclusion: D-ribose is active in glycation and induces protein aggregation, rapidly producing AGEs in vitro and in vivo.
General significance: Ribosylation, leading to the production of significant amounts of AGEs both extracellularly and intracellularly, may be involved in cell dysfunction and subsequent cognitive impairments. This review may be a useful reference for studies on the pharmacokinetics of D-ribose action.

1. Introduction

D-ribose, an aldopentose discovered in 1891 by Emil Fischer, has an aldehyde active group in its open chain form and is present in living cells, playing an important role in life processes. While this monosaccharide is a monomer subunit of RNA and is considered to be an important component in the origin and earliest steps of life, its prebiotic availability is still under investigation [1,2]. D-ribose is the structural backbone of purines and pyrimidines, critical cellular compounds which are components of genetic material, and is a constituent of, numerous cofactors, certain vitamins, and adenosine triphosphate (ATP) the "energy currency" of the cell. In the D-ribose metabolic pathway, this furanose is phosphorylated to D-ribose-5-phosphate, a precursor in nucleotide, histidine, and tryptophan synthesis. Every cell needs D-ribose for essential activities. D-ribose can be obtained from the diet, especially from foods containing high amounts of riboflavin, and can be absorbed into the bloodstream from the oral cavity and intestinal tract. The levels of D-ribose in the blood and the cerebrospinal fluid are 0.01–0.1 mM in healthy individuals [3,4]. Endogenous D-ribose can be produced from glucose via the hexose monophosphate shunt and is released from nucleotides during metabolic turnover. Free D-ribose can also appear as an intermediate in nucleotide metabolism. Utilization of external D-ribose for replenishing cellular levels of adenine nucleotides requires transport of D-ribose across the plasma membrane [5].

D-ribose actively participates in protein glycation both inside (endogenous glycation) and outside the body (exogenous glycation) because of its reducing ability. In recent years, ribosylation has attracted more attention due to its role in protein glycation and its subsequent effects such as protein aggregation and reactive oxygen species (ROS) production [6–8]. Glycation is a reaction which occurs in all cell types and organisms. Glycated products slowly accumulate in vivo leading to protein dysfunction, and are involved in the aging process and the progress of some diseases. Although high level ribose has not been found in a common disease, a rare disease called ribose-5-phosphate isomerase deficiency shows an increase in the polyols arabitol, ribitol and erithrol with a white matter disorder according to van der Knaap et al. [9,10]. Furthermore, it has been reported that poly(ADP-ribosyl)ation of nuclear protein increases in Alzheimer's disease [11]. Here we provide an overview of the action of D-ribose in glycation and protein aggregation.

2. D-ribose is highly reactive in glycation

In general, all reducing sugars can participate in glycation reactions. Fig. 1 shows an example of a reaction of D-ribose with a lysine residue in

Abbreviations: AGEs, advanced glycation end products; CML, carboxymethyllysine; ROS, reactive oxygen species; BSA, bovine serum albumin; HAS, human serum albumin; RAGE, receptors for advanced glycation end products; CD, circular dichroism

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a protein and subsequent reactions leading to the production of the AGE carboxymethyllysine (CML). According to their chemical structure, reducing sugars may be divided into two groups: furanoses and pyranoses. The glycating ability of the former is stronger than that of the latter, possibly because the pentose ring is not planar but occurs in one of a variety of conformations generally described as "puckered", which causes the unstable aldofuranose ring vulnerable to reactions with amino groups [12,13]. Of the reducing sugars, D-ribose is the most reactive in the glycation of proteins. The glycating ability of reducing sugars was thought to increase in the following order: D-glucose<D-mannose<D-galactose<D-xylose<D-fructose<D-arabinose<D-ribose<2-deoxy-D-ribose [14]. However, Wei and colleagues, using BSA to compare the glycating ability of different reducing sugars, have shown that furanoses, such as D-ribose and D-xylose, glycate BSA more rapidly than pyranoses, such as D-glucose and D-fructose [12]. Other research groups have also used D-ribose and albumin to study the generation of glycation products. Syrovy studied albumin glycated using four different reducing sugars and determined the extent of glycation by four different methods. Results showed that D-ribose was more active in glycation than the other sugars used [15]. Culbertson and colleagues used D-ribose and BSA to produce AGEs. They measured the effect of inhibitors on AGE formation and found that Amadori decomposition pathway was constrained in the presence of metal ion chelators and radical traps [16]. Bokiej and coworkers showed that the glycation of horse heart metmyoglobin with D-ribose and its derivatives (D-ribose-5-phosphate and 2-deoxyribose-5-phosphate) results in the cross-linking of this protein [17].

Serum albumin comprises about 60% of human plasma protein and its concentration is the major contributor to the oncotic pressure of blood. It is particularly highly sensitive to glycation and the effect of glycation on serum albumin is marked. In vivo, the proportion of glycated albumin in healthy persons is in the range between 1% and 10% [18,19]. However, in individuals with hyperglycemia it can increase two- to three-fold [20,21]. For this reason serum albumin has been adopted as a model in many in vitro studies on glycation [12,15,16].

While the glycation reaction occurs extensively in all tissues of the human body, it is of particular importance in the blood. Reducing sugars slowly and continuously glycates proteins in the blood, including almost all kinds of plasmatic proteins, such as hemoglobins, immunoglobulins, and proteins from the extracellular matrix, such as collagen, laminin and fibronectin. The glycation process occurs over a relatively long time under normal conditions, but is accelerated with increasing age and during the course of various diseases.

3. AGEs and disease

Advanced glycation end products (AGEs) have been investigated extensively because of their involvement in many diseases such as diabetes [22], cataracts [23], renal failure [24], and other disorders [25]. Intracellular AGEs have also been associated with physiological aging [26] and neurodegenerative diseases such as Alzheimer's disease [27], Parkinson's disease [28] and amyotrophic lateral sclerosis (ALS) [29]. The study of AGEs has become one of the most important areas of biochemical research today. In addition, many studies have shown that glycation leads to the production of ROS, which are harmful in cellular metabolism and cause cell damage [30–33]. Considerable attention has been paid to studying the production of hydroxyl radicals via glycation, and inhibition of subsequent damage caused by them [34,35].

The relationship between the accumulation of AGEs and neurodegenerative disease, such as cognitive impairment, is the subject of active investigation. Multiple studies have suggested that AGEs are directly neurotoxic to cultured neurons [36,37]. AGEs and their precursors (methylglyoxal and glyoxal) increase the aggregation and cytotoxicity of intracellular amyloid-beta carboxy-terminal fragments [38]. When AGEs interact with receptors for advanced glycation end products (RAGEs), an array of signal transduction cascades are activated [39]. AGEs may be involved in the generation of ROS and inflammation via their interaction with RAGEs, and may play a role as activating factors for neuroglia cells such as astrocytes or microglias [40,41], inducing them to produce cytotoxic cytokine-like molecules which then may induce further neuronal cell injury and death and dysfunction of the brain. However, whether AGEs induced by D-ribose are the same as those generated spontaneously in vivo, and the mechanism by which

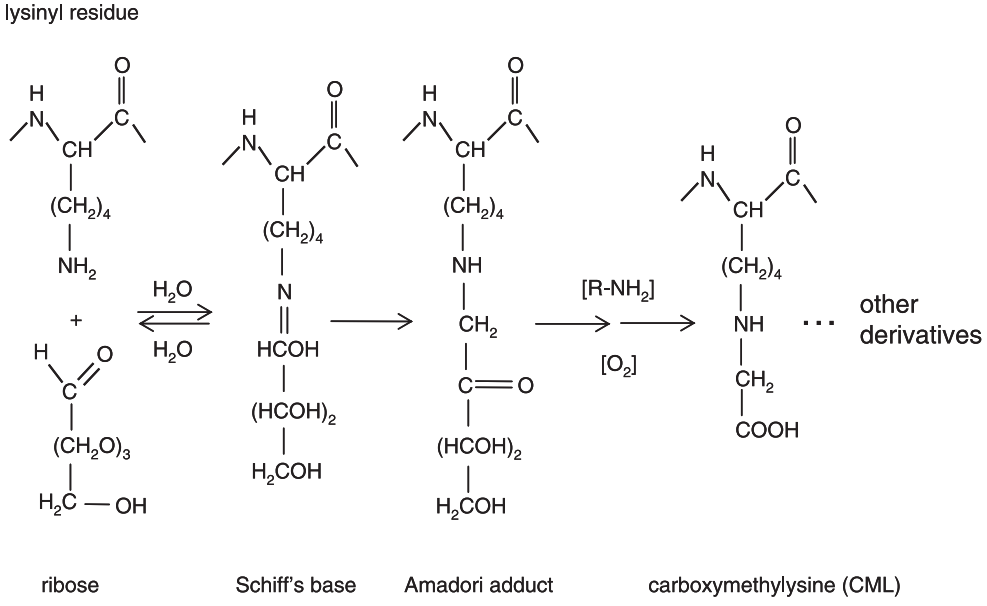

Fig. 1. D-ribose-induced AGE formation. Glycation is a spontaneous process between the free amino group of a protein (in this case lysine) or lipid molecule and the carbonyl group of a reducing sugar (in this case D-ribose), without the controlling action of an enzyme (sometimes called non-enzymatic glycosylation). It begins with the formation of a reversible intermediate product (Schiff's base). The Schiff's base becomes a stable ketoamine after an Amadori rearrangement. The final step is the formation of irreversible products called advanced glycation end products (AGEs), such as carboxymethyllysine (CML), pentosidine, pyrraline, carboxyethyllysine (CEL), and imidanolone.

D-ribose-induced AGEs impair spatial learning and memory, needs further investigation.

D-ribose has also been adopted for research on the glycation of other proteins and their resultant AGEs [42–44]. Paul and colleagues studied the characterization of AGEs derived from the in vitro reaction of ribose and collagen, and successfully isolated two low-molecular-weight components, αNFC-1 [N^{δ}-(4-oxo-5-dihydroimidazol-2-yl)-L-ornithine] and βNFC-1 a 4-imidazolon-2-yl derivative existing in three tautomeric forms [45]. Verbeke and colleagues incubated BSA with D-ribose and other reducing sugars and tested the ability of N^6-furfuryladenine (kinetin) to protect against oxidative and glycoxidative protein damage in vitro. They found that kinetin inhibited AGE formation and limited the aggregation of BSA during glycation [46]. Luciano et al. incubated ribose with fetal calf serum to generate glycation products and found that glycated fetal calf serum is toxic to insulin-secreting cells and increases intracellular oxidative stress [47]. From these reports we can see that the high reactivity of D-ribose has led to its widespread use as a glycating reagent for research in AGE-related diseases.

4. Ribosylation induces protein aggregation

During the process of glycation, in addition to the classical steps (Schiff's base generation, Amadori rearrangement and AGE formation), formation of molten globule-like protein aggregates has also been reported to occur during the progression of glycation reactions. Several research groups have demonstrated a link between protein aggregation and glycation as the duration of the glycation reaction increases [48,49]. Sattarahmady and coworkers incubated human serum albumin (HSA) with D-glucose, and detected the formation of AGEs using different techniques. They observed that the Maillard reaction causes HSA to form a molten globule-like state [50]. The multimerization or condensation of glycated proteins into plaque has been observed for extracellular matrix proteins such as fibrinogen, collagen and other circulating proteins [51].

Recent work has also shown that BSA forms globular amyloid-like aggregations on glycation with D-ribose [12]. Compared with other reducing sugars, D-ribose glycates proteins such as BSA, Tau and α-Synuclein rapidly and induces them to form globule-like deposits [36,52]. In the glycation of α-Synuclein, an important protein involved in neurodegenerative disease, D-ribose reacts with lysinyl residues in the C-terminal region and then the N-terminal region, leading to protein polymerization and aggregation (Fig. 2).

Although glycation with D-ribose results in protein aggregation, research in our lab indicates that alterations in tertiary structure during the glycation process of BSA with D-ribose do not impact the secondary structure of this protein during incubations lasting up to one week [12]. Incubation of α-Synuclein or Tau protein with D-ribose, for example, leads to the formation of molten globule-like aggregations without α-helices/β-sheets as observed by circular dichroism (CD) [36,52,53]. Prolonged incubation (over 7 weeks) of HSA with ribose induces its transition from a helical structure to β-sheets, the basic structure involved in amyloid formation. Twenty weeks of incubation of HAS with ribose induces significant amyloid nanofibril formation [48]. However, the mechanism underlying glycation-induced amyloid formation and conformational changes requires further clarification.

5. Ribosylation and cytotoxicity

On culturing human quiescent peripheral blood mononuclear cells with D-ribose and 2-deoxy-D-ribose, Barbieri and colleagues were the first to observe that these two sugars can induce apoptosis [54]. Kaneto and coworkers induced apoptosis in isolated rat pancreatic islet cells and the pancreatic β-cell derived cell line HIT by adding reducing sugars D-fructose and D-ribose. They demonstrated that reducing sugars trigger oxidative modifications and apoptosis by oxidative stress via glycation

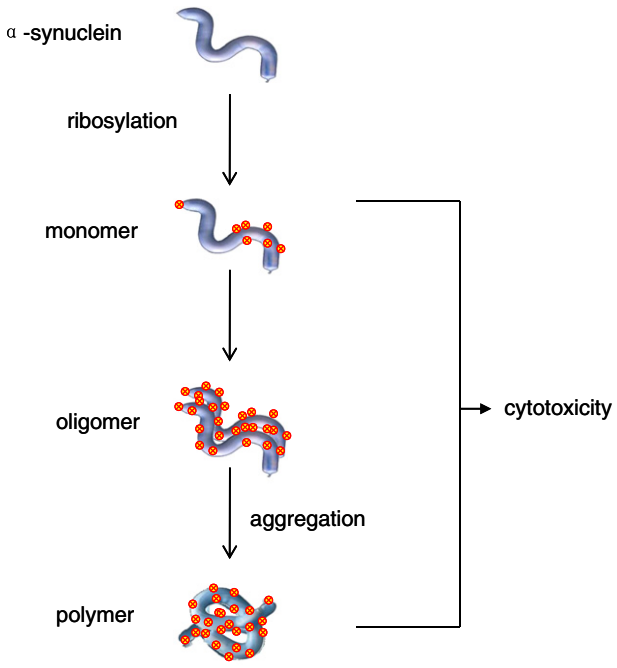

Fig. 2. A putative scheme for the aggregation of ribosylated protein into highly cytotoxic molten globules. Glycation of α-Synuclein with D-ribose induces protein misfolding and results in the formation of aggregations with high cytotoxicity.

[55]. A retinoic acid-induced HL-60 cell differentiation culture model was adopted and the addition of D-ribose (10–25 mM) was shown to reduce cell proliferation and lead to apoptosis [56]. According to our recent work, 10 mM D-ribose enhances the intracellular yield of AGEs in cultured HEK293T cells, SH-SY5Y cells, and primary cultured hippocampal neurons, and leads to a reduction in viability [57].

In addition, the effects of 2-deoxy-D-ribose on cells have also been studied by several groups. Koh and colleagues induced cytotoxicity and apoptosis by incubating HIT-T15 cells with 2-deoxy-D-ribose for 24 h. 2-deoxy-D-ribose increased levels of intracellular ROS and protein carbonyl levels. Three antiglycating agents (diethylenetriaminepentaacetic acid, aminoguanidine, and pyridoxamine) were shown to decrease the production of intracellular protein carbonyls induced by 2-deoxy-D-ribose [58]. Lee and coauthors observed that kaempferol protects β-cells from 2-deoxy-D-ribose-induced oxidative damage, apoptosis and lipid peroxidation [59]. In research on the effect of fructosamine-3-kinase (FN3K) on the function and survival of mouse pancreatic islets after culture at high concentrations of D-ribose, Pascal and coworkers found that FN3K deficiency improves β-cell survival and function while reducing the glycation of intracellular islet proteins [60].

All the aforementioned work was performed on the assumption that D-ribose is cytotoxic. However, D-ribose also has protective effects under certain conditions. 2-deoxy-D-ribose inhibits hypoxia-induced apoptosis in human leukemia HL-60 cells, possibly by inhibiting the p38 signaling pathway [61]. Simultaneous administration of creatine and D-ribose confers anti-ischemic protection via the Akt and AMPK signaling pathways [62]. These differences in the effect of D-ribose may depend on its cellular concentration, the duration of exposure, and on cell culture conditions. It seems that a proper concentration of D-ribose has protective effects when cells are under deleterious conditions, but excess D-ribose promotes the deterioration of cells when cells are in normal culture conditions,

6. Ribosylation leads to the dysfunction of organs and cognitive impairments

Most recent research has shown that D-ribose has a positive effect when used in the treatment of many diseases and provides protection

under physiologically deleterious conditions. Seifert and colleagues tested the effect of D-ribose on markers of free radical production (urinary malondialdehyde and plasma reduced glutathione) during hypoxic exercise in a double-blinded, crossover study. D-ribose administration showed a beneficial effect in lowering malondialdehyde and glutathione levels during hypoxic stress [63]. D-ribose is also recommended as a supplement for the metabolic support of the heart [64]. In cardiovascular diseases, the failing heart is energy-starved and D-ribose is believed to replenish deficient cellular energy levels and improve depressed function [65]. D-ribose treatment reduces the infarct size and improves heart function after myocardial infarction in rats [66]. It also shows protective effects against renal injury caused by ischemia and reperfusion in rats with transient hyperglycemia [65]. A pilot study conducted by Jacob and colleagues to evaluate if D-ribose could improve symptoms in fibromyalgia and/or chronic fatigue syndrome patients indicated that D-ribose significantly reduces clinical symptoms in patients suffering from these conditions [67]. In addition, D-ribose can reverse the inhibition of larval growth by D-psicose in *Caenorhabditis elegans* [68].

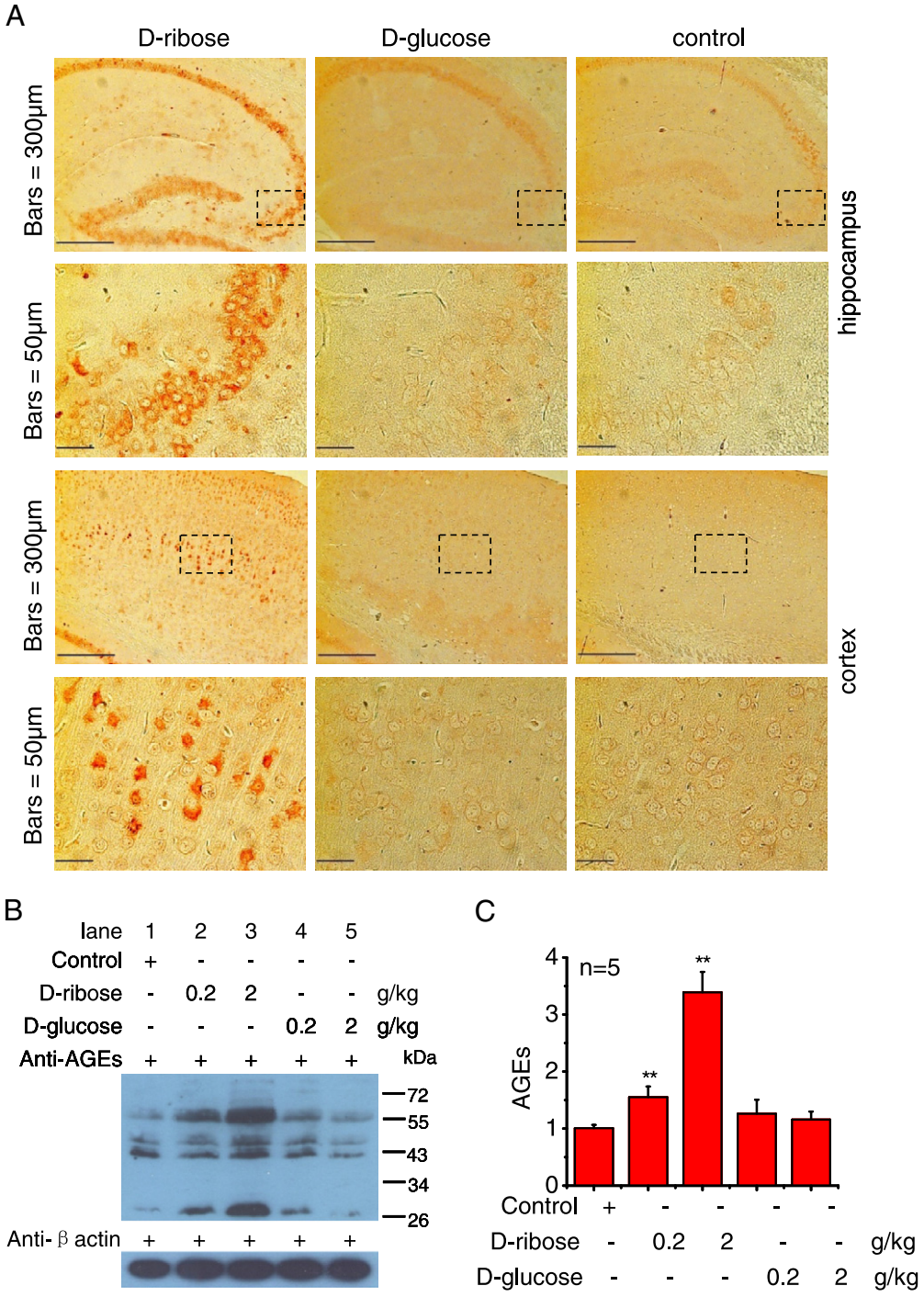

Fig. 3. AGE levels in the mouse brain increase after injection with D-ribose. Mice were injected (i.p.) with either D-ribose at a dose of 0.2 g/kg, 2 g/kg, or D-glucose at dose of 0.2 g/kg, 2 g/kg, or 0.9% saline (controls) for 30 days. AGEs in the mouse brain were detected by immunohistochemistry using an anti-AGE monoclonal antibody. The areas outlined with dashed lines are magnified (panel A). AGEs in the mouse brain detected by Western blotting using anti-AGEs (6D12 monoclonal antibody, panel B), with β-Actin used as a loading control. Quantification results are shown in panel C. The saline control value was set as 1.0. All values are expressed as means ± S.E.M. *$P<0.05$, **$P<0.01$. These data were referred to Han et al., PLoS ONE, 2011, 6(9):e24623 [57].

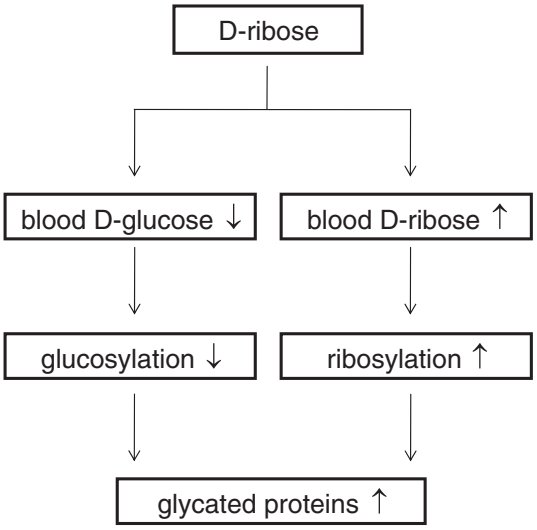

Fig. 4. Effect of administration of D-ribose on glyation of blood protein. Administration of D-ribose lowers the blood glucose, leading to hypoglycemia [70–72]. However, under this condition, an increase of glycated plasma protein was significantly observed [57]. The increased glycated protein in blood resulted from ribosylation though the concentration of blood glucose decreases.

According to the aforementioned reports, the protective effect of D-ribose is due to its ability to replenish cellular energy levels. However, Dhanoa and Housner have pointed out that while D-ribose supplementation leads to enhanced restoration of ATP levels following exercise, this is seldom translated into increased athletic performance [69]. D-ribose can cause hypoglycemia in mammals including man, rabbits and dogs [70–72]. Sloviter and Petkovic were the first to report that infusion of rabbits with D-ribose causes an increase in plasma insulin concentration [73], and suggested that the secretion of insulin may explain the hypoglycemia caused by D-ribose. Our data have also shown that intraperitoneal injection of D-ribose elevates the level of glycated proteins and accelerates the formation of AGEs in the serum of mice. The administration of high levels of D-ribose over a relatively long period leads to a high yield of AGEs in the mouse brain and is accompanied by impairment of learning and memory ability (Fig. 3) [57]. Based on reports and our research results, administration of D-ribose increases blood D-ribose, accompanied with hypoglycemia. In fact, administration of D-ribose accelerates the progression of nonezymatic ribosylation, leading to an increase of glycated protein in blood (Fig. 4). So far, the mechanism of blood glucose lowering effect induced by D-ribose has not been fully elucidated. The hypoglycemia effect of D-ribose appears to result from a combination of factors including indirect stimulation of pancreatic insulin secretion, stimulation of humoral effectors causing secretion of insulin from tissues, and delayed glucose recruitment in the liver [74–76].

Here, we propose a mechanism for the biological effects of D-ribose (Fig. 5). While D-ribose is an essential molecule in the cell, it also triggers the glycation process both outside and inside cells, resulting in the aggregation of AGEs which induce cell dysfunction.

In conclusion, D-ribose administration can induce hypoglycemia and increased insulin concentration, it also participates in glycation reaction which leads to cross-linking of proteins in the formation of detergent-insoluble and protease-resistant aggregates, and affects the biological functions of proteins. Risks associated with the use of D-ribose should thus be taken into consideration, particularly in the long term administration of D-ribose. However, D-ribose, as a bioactive ingredient, has been used in nutrition and medicine for a long time, but the side effect of its administration is not well known. Thus, the effect of ribosylation on human body should be examined regularly. It may be a practicable mean to monitor the blood glycated proteins in those patients of D-ribose administration.

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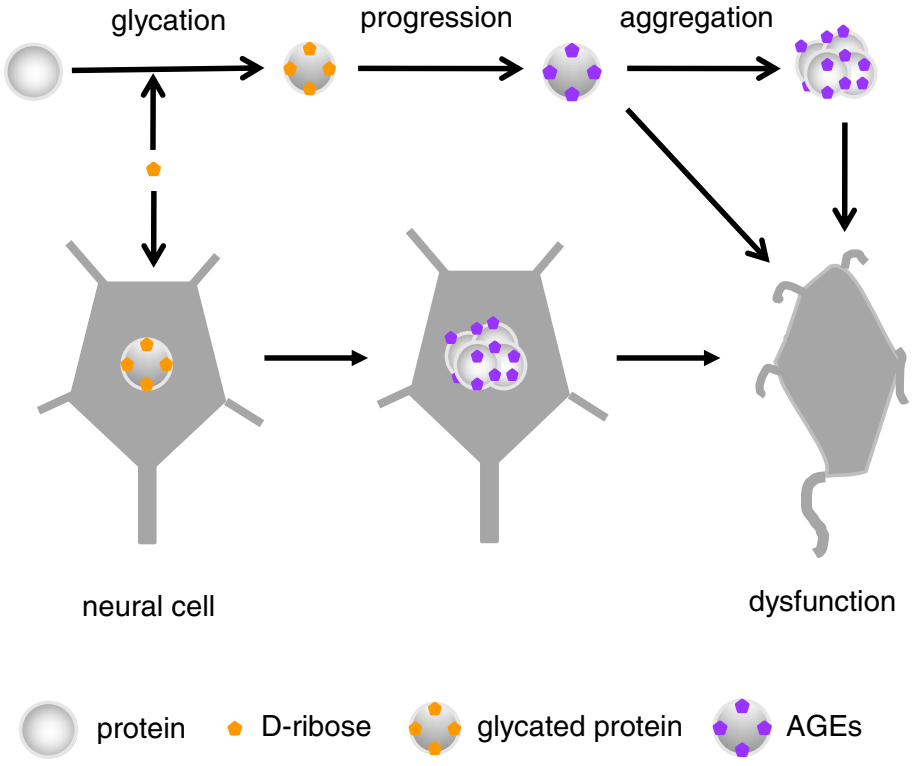

Fig. 5. Proposed mechanism for the biological effects of D-ribose. D-ribose triggers both extracellular and intracellular glycation, resulting in the generation of AGEs which then aggregate. AGEs are toxic to the cell and induce cell dysfunction.

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Conflict of interest statement

The authors declare that there are no competing interests.

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