Received: 9 October 2017 | Accepted: 16 January 2018

DOI: 10.1002/ame2.12001

REVIEW ARTICLE

Redox imbalance stress in diabetes mellitus: Role of the polyol pathway

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Funding information
National Institutes of Health, Grant/Award Number: R01NS079792; UNTHSC Seed Grants, Grant/Award Number: RI10015 and RI10039

Abstract

In diabetes mellitus, the polyol pathway is highly active and consumes approximately 30% glucose in the body. This pathway contains 2 reactions catalyzed by aldose reductase (AR) and sorbitol dehydrogenase, respectively. AR reduces glucose to sorbitol at the expense of NADPH, while sorbitol dehydrogenase converts sorbitol to fructose at the expense of NAD^+, leading to NADH production. Consumption of NADPH, accumulation of sorbitol, and generation of fructose and NADH have all been implicated in the pathogenesis of diabetes and its complications. In this review, the roles of this pathway in NADH/NAD^+ redox imbalance stress and oxidative stress in diabetes are highlighted. A potential intervention using nicotinamide riboside to restore redox balance as an approach to fighting diabetes is also discussed.

KEYWORDS
diabetes mellitus, fructose, NADH/NAD^+, oxidative stress, polyol pathway, redox imbalance stress

1 | INTRODUCTION

Diabetes mellitus is a debilitating disease. It impairs the biological function of many organs in the body. The underlying mechanism of diabetic pathogenesis is hyperglycemia-induced chronic glucotoxicity,[1-6] which impairs numerous pathways in the biological metabolome. During development and progression of diabetes, many pathways are upregulated in an attempt to handle the overflow of glucose in the body. These pathways include the polyol pathway,[7-12] the glycation pathway,[13-15] the protein kinase c pathway,[16-19] the hexosamine pathway,[20-22] and the enediol/alpha-ketoaldehyde pathway.[23-25] It is now believed that all the pathways converge on elevation of reactive oxygen species (ROS) by a variety of ROS generation systems.[25-28]

Under normoglycemic conditions, the major purpose of glucose combustion is to produce energy in the form of ATP, and to produce NADPH and ribose via the pentose phosphate pathway (Figure 1A). Excess glucose can be further stored in the body as either glycogen or fatty acids (Figure 1A).[29] As glucose metabolism involves electron extraction, storage, and transportation, nearly all the biochemical reactions in glucose metabolism are actually redox reactions. For example, splitting of glucose to 2 molecules of pyruvate during glycolysis stores the extracted electrons in NADH, as does the pyruvate dehydrogenase complex pathway whereby pyruvate is decarboxylated to form acetyl-CoA. After entry of acetyl-CoA into the Krebs cycle, electrons are stored in both NADH and $FADH_2$. These electron donors then donate their electrons to complex I (NADH) or complex II ($FADH_2$) in the mitochondrial electron transport chain. Oxygen is only used at the last step whereby complex IV transports electrons from cytochrome c to oxygen.

As glucose provides electrons that are mainly stored in NADH, the higher the blood glucose levels, the higher the NADH contents. This can tilt the redox balance between NADH and NAD^+ toward the side of NADH, resulting in redox imbalance.[6,30] This is indeed what occurs in diabetes[31,32] and the polyol pathway is known to

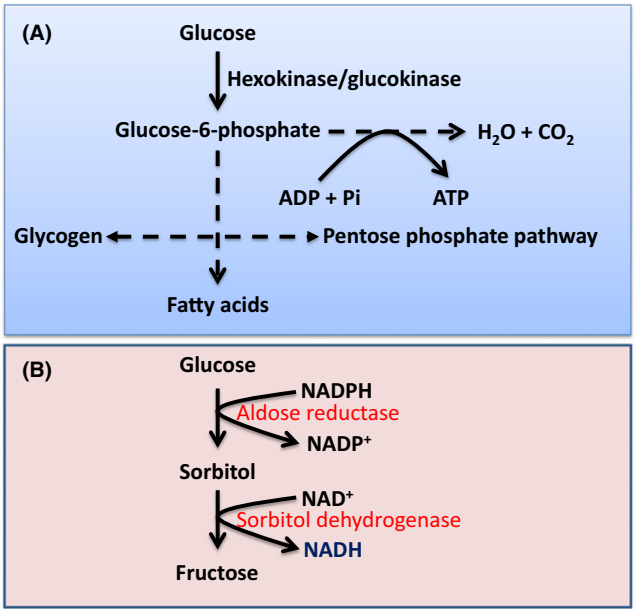

FIGURE 1 Glucose metabolic pathways under euglycemic and hyperglycemic conditions. A, Under normal physiological conditions, glucose is used for energy (ATP) production via glycolysis and the Krebs cycle pathways. Glucose can also be fluxed to the pentose phosphate pathway that makes NADPH and ribose. Excess glucose can be stored as glycogen or fatty acids. B, Under diabetic conditions, approximately 30% of glucose can be fluxed to the polyol pathway, whereby glucose is converted to fructose via 2 consecutive reactions that also transform NADPH to NADH

play a major role in breaking the redox balance between NADH and NAD^+.[33-36]

2 | THE POLYOL PATHWAY

The polyol pathway consists of 2 reactions catalyzed by 2 respective enzymes.[7,10,35] As shown in Figure 1B, the first reaction is reduction of glucose to sorbitol, which is catalyzed by aldose reductase (AR). This reaction is the rate-limiting reaction[37] in this pathway and also converts NADPH to $NADP^+$. The second reaction converts sorbitol to fructose and is catalyzed by sorbitol dehydrogenase, which makes NADH from NAD^+. So the overall products of the polyol pathway are sorbitol, fructose, and NADH. NADH production results from the consumption of NADPH. Because nearly 30% of blood glucose can flux through the polyol pathway in diabetes,[38,39] this pathway has been thought to be the major pathway contributing to NADH/NAD^+ redox imbalance in diabetes.[7,8,26,34] I will now dissect each of the pathway's components (Figure 2) and their role in redox imbalance stress and diabetes mellitus.

2.1 | Aldose reductase

The physiological function of this enzyme still remains murky, but it is usually thought that the enzyme, under normal physiological

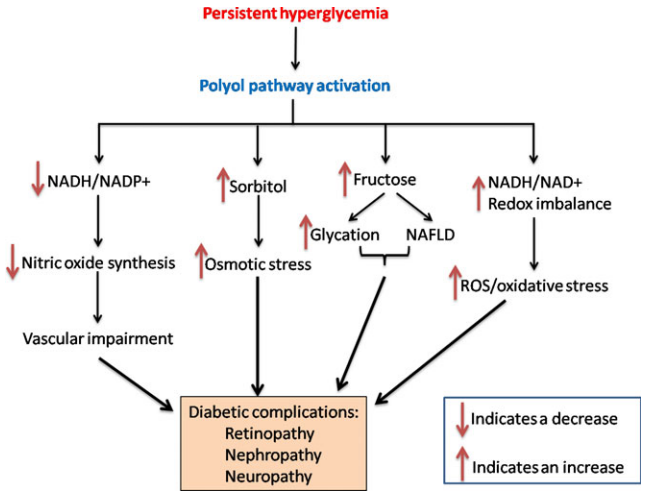

FIGURE 2 Pathophysiological effects of the polyol pathway activated by persistent hyperglycemia. Activation of the polyol pathway can (1) decrease the NADPH/$NADP^+$ ratio and nitric oxide production; (2) induce sorbitol accumulation and osmotic stress; (3) increase fructose content, leading to increased protein glycation and development of non-alcoholic fatty liver disease (NFALD); (4) increase NADH/NAD^+ ratio leading to ROS production and oxidative stress. The consequences of these events are diabetic complications including retinopathy, nephropathy, and neuropathy

conditions, can degrade toxic aldehyde byproducts formed by lipid peroxidation such as 4-hydroxy-nonenal (HNE) and its glutathione conjugates (GSH-HNE).[40,41] However, its ability to catalyze glucose reduction is nearly negligible under physiological conditions due to the high K_m of its reaction with glucose.[42] In contrast, when the glucose level is high, this enzyme and the polyol pathway becomes a major pathway in disposing of glucose.[7,35-37,43]

The role of AR in diabetes has been well elucidated by using its inhibitors and by AR knockout animal models. It has been found that AR inhibitors can ameliorate diabetes mellitus.[44,45] In fact, numerous AR inhibitors have been tested and evaluated.[46-50] For example, the AR inhibitor zopolrestato can lower acetate utilization in the diabetic heart,[45] indicating increased glucose combustion via the glycolytic pathway and the Krebs cycle, that otherwise is inhibited in diabetes. Another example is the use of AR inhibitor sorbinil,[51] which has been clinically used to stabilize diabetic corneal epithelial disorders.[52] One caveat of inhibiting the polyol pathway is that it could be over-inhibited, leading to increased protein glycation by glucose.[53]

With respect to AR deletion or knockout studies, it has been demonstrated that AR deletion from mice could inhibit diabetes-induced retinal capillary degeneration mediated by superoxide production.[54] It has also been demonstrated that the AR knockout mouse is resistant to the development of diabetic nephropathy.[55]

2.2 | Consumption of NADPH and redox imbalance of NADPH and $NADP^+$

As glucose flux through the polyol pathway consumes NADPH, it has been suggested that the level of NADPH could be significantly

decreased.[56] Indeed, we have found that this is the case in diabetic lung and pancreas,[31,57] whereby NADPH content is lower than that in controls. It has been established that there is about a 15% decrease in NADPH in the diabetic lens.[35] The NADPH decrease could further impair the GSH/GSSG redox balance, as GSSG reduction by glutathione reductase requires NADPH as a cofactor.[58,59] NADPH is also involved in the biosynthesis of biological molecules such as fatty acids and nitric oxide, so its decrease or depletion should have deleterious effects on many anabolic pathways.[60] Additionally, from a chemical point of view, the polyol pathway can also compete with glutathione reductase for NADPH,[61,62] leading to further impairment in glucose metabolism.

2.3 | Accumulation of sorbitol

In certain tissues such as retina, sorbitol dehydrogenase content is low,[63] so sorbitol formed from glucose reduction can accumulate.[35] This accumulation can change cellular membrane osmotic pressure and triggers osmotic stress.[35] This osmotic stress has been thought to be the main underlying mechanism for diabetic retinopathy[64,65] and has also been implicated in diabetic kidney dysfunction or nephropathy.[9] It should be noted that even in the same organ, different cell populations may have different levels of sorbitol dehydrogenase;[66] hence, the effect of sorbitol on diabetic tissue is differential.

2.4 | NADH overproduction and NAD^+ depletion

The second reaction of the polyol pathway involves NADH production from NAD^+. This pathway has therefore been regarded as the major source of NADH/NAD^+ redox imbalance.[5,6,26,32] On one hand, NADH is overproduced, which could lead to reductive stress followed by oxidative stress.[26,28] This is because elevated levels of NADH could overwhelm mitochondrial complex I, leading to more ROS production from the mitochondrial electron transport chain.[26] Additionally, excess NADH can also inhibit the glycolytic pathway, the pyruvate dehydrogenase complex, and the Krebs cycle,[12,67] leading to more flux of glucose through the polyol pathway. On the other hand, an NAD^+ decrease also imposes deleterious effects on a variety of metabolic pathways.[6] A major one is the sirtuin pathway,[6] which is responsible for protein deacetylation.[68] A decrease in NAD^+ would inactivate sirtuins, leading to over-acetylation of proteins and less efficient glucose metabolism.[69-71]

In the case of NADH/NAD^+ redox imbalance, it has been demonstrated that restoring the redox balance by supplementing with an NAD^+ precursor or analogue is a valuable approach.[72] In this regard, the recently identified precursor nicotinamide riboside is very promising as this chemical is more tolerant and has fewer side-effects than niacin.[73] For example, it has been reported that nicotinamide riboside can ameliorate diabetes and diabetic neuropathy in mice, and can enhance metabolism and prevent development of obesity induced by a high fat diet.[74,75]

2.5 | Fructose

As the polyol pathway consumes approximately 30% of blood glucose in diabetes,[39] fructose is overproduced in the body. Overproduction of fructose can lead to severe metabolic consequences. On one hand, fructose can chemically glycate proteins,[76] leading to protein dysfunction. It is known that fructose can be further metabolized to produce 3-deoxyglucose and fructose-3-phosphate, both of which are very potent nonenzymatic glycation agents.[76] On the other hand, as fructose metabolism by fructokinase, with the consumption of ATP, can bypass the regulation of the glycolytic pathway,[77,78] acetyl-CoA could be overproduced[78] and ATP could be depleted.[79] Acetyl-CoA overproduction could cause non-alcoholic fatty liver disease (NAFLD), as acetyl-CoA is the precursor of fatty acid,[77,80-82] while ATP depletion could cause cell death. Additionally, overproduction of acetyl-CoA can result in more protein acetylation, leading to protein functional impairment.[83-85] Protein acetylation can worsen when sirtuin proteins are inactive due to lack of NAD^+ in diabetes.[6,86] Therefore, fructose accumulation due to activation of the polyol pathway by hyperglycemia can accentuate diabetes and its complications.

2.6 | Effect of redox imbalance on sirtuins

Sirtuins are protein deacetylases that use NAD^+ as their substrate.[87] So when NAD^+ levels decrease during diabetes, sirtuin activities will be decreased,[69,88] and this can also be modulated by decreased expression of sirtuin proteins. Indeed, numerous studies including ours, have demonstrated attenuated expression of sirtuin proteins in diabetes.[31,57,88,89] As a consequence, protein acetylation is increased (Figure 3A), leading to functional changes of numerous proteins.[83,90] Accordingly, studies have demonstrated that supplementing with NAD^+ precursors or analogous can serve as an approach for enhancing sirtuin activity, thereby augmenting protein deacetylation, which can lead to amelioration of diabetes.[70,71,91]

2.7 | Effect of redox imbalance on poly-ADP-ribosylase function

In diabetes, it is usually thought that DNA damage occurs first, which triggers the upregulation of poly-ADP-ribosylase (PARP) activity.[32,92,93] This upregulation can deplete NAD^+, as PARP also uses NAD^+ as its substrate during repair of damaged DNA.[94-96] Indeed, PARP knockout mouse has been found to be resistant to diabetes development[97,98] and inhibition of PARP can also retard the development of diabetes.[99-102] On the other hand, it is also possible that decreased levels of NAD^+ caused by activation of the polyol pathway could impair PRAP activity, leading to accentuation of diabetes, as it is likely that damaged DNA would not get repaired promptly. Nonetheless, the crosstalk between the polyol pathway and the PARP pathway will need to be further investigated. This author tends to believe that the 2 pathways may form a vicious cycle that will worsen the situation during progression of diabetes.

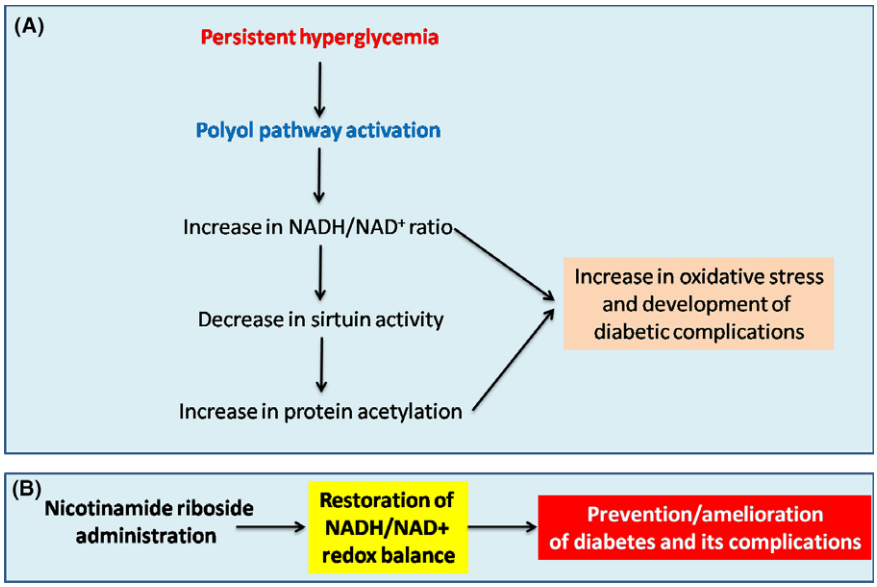

FIGURE 3 A, NADH/NAD$^+$ redox imbalance induced by activation of the polyol pathway can attenuate sirtuin activity and increase protein acetylation which eventually leads to oxidative stress and development of diabetic complications. B, Restoration or normalization of NADH/NAD$^+$ redox balance by nicotinamide riboside, which can serve as a promising approach to preventing or ameliorating diabetes and its complications

2.8 | Redox imbalance and oxidative stress

One of the major consequences of NADH/NAD$^+$ redox imbalance is oversupply of electron donors to the mitochondrial electron transport chain.[26] Oversupply of NADH would overwhelm complex I, which relays electrons from NADH to CoQ.[32] One feature of complex I electron transport is that the more electrons it transports, the more superoxide it will produce.[103-106] This is because more electrons could leak and partially reduce oxygen, leading to overproduction of superoxide which is the precursor of all the ROS.[107-110] Hence, oversupply of NADH in diabetes driven by constant hyperglycemia can devastate cells with enhanced oxidative stress, impaired mitochondrial function, and increased cell death, as has been demonstrated by numerous investigators.[17,27,28,111-118]

2.9 | Targeting redox imbalance as an approach for diabetes therapy

It is reasonable to say that diabetes is a redox imbalance disease.[32] Hence restoration of NADH/NAD$^+$ redox balance may serve to combat diabetes. One approach, as mentioned above, is supplementing with NAD$^+$ precursors or analogues (Figure 3B). In particular, the utilization of nicotinamide riboside in a variety of experimental settings has demonstrated the beneficial effects of this compound.[10,74,75,119] Additionally, plant extracts or compounds that are antioxidants in nature have also been evaluated for their effects in mitigating oxidative stress and promoting cell survival.[120-123] As these compounds can counteract the deleterious effects of the activated polyol pathway that is responsible for redox imbalance in diabetes, an understanding of how they work in alleviating diabetes and its complications should provide insights into the design of novel strategies for fighting this epidemic and devastating disease.

3 | CONCLUDING REMARKS

The active polyol pathway in diabetes mellitus is a major contributor to NADH/NAD$^+$ redox imbalance due to its ability to convert NADPH to NADH. Not only can excess NADH induce oxidative stress via generation of ROS through the mitochondrial electron transport chain and other pathways, but lowered NADPH content can also induce oxidative stress by impairing glutathione metabolism. Approaches to restoration of redox balance by targeting the polyol pathway have been explored and should remain a research focus in order to provide novel strategies for fighting diabetes and its complications.

ACKNOWLEDGEMENTS

The writing of this review article was supported in part by UNTHSC seed grants RI10015 and RI10039 and by the National Institutes of Health (grant no. R01NS079792).

CONFLICT OF INTEREST

None.

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How to cite this article: Yan LJ. Redox imbalance stress in diabetes mellitus: Role of the polyol pathway. *Anim Models Exp Med*. 2018;1:7–13. https://doi.org/10.1002/ame2.12001