

# Role of pseudohypoxia in the pathogenesis of type 2 diabetes

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Jing Song<sup>1,2</sup>  
Xiaojuan Yang<sup>1,3</sup>  
Liang-Jun Yan<sup>1</sup>

<sup>1</sup>Department of Pharmaceutical Sciences, UNT System College of Pharmacy, University of North Texas Health Science Center, Fort Worth, TX, USA; <sup>2</sup>School of Public Health, Shanxi Medical University, Taiyuan, People's Republic of China;

<sup>3</sup>Department of Geriatrics, First Hospital/First Clinical Medical College of Shanxi Medical University, Taiyuan, People's Republic of China

**Abstract:** Type 2 diabetes is caused by persistent high blood glucose, which is known as diabetic hyperglycemia. This hyperglycemic situation, when not controlled, can overproduce NADH and lower nicotinamide adenine dinucleotide (NAD), thereby creating NADH/NAD redox imbalance and leading to cellular pseudohypoxia. In this review, we discussed two major enzymatic systems that are activated by diabetic hyperglycemia and are involved in creation of this pseudohypoxic condition. One system is aldose reductase in the polyol pathway, and the other is poly (ADP ribose) polymerase. While aldose reductase drives overproduction of NADH, PARP could in contrast deplete NAD. Therefore, activation of the two pathways underlies the major mechanisms of NADH/NAD redox imbalance and diabetic pseudohypoxia. Consequently, reductive stress occurs, followed by oxidative stress and eventual cell death and tissue dysfunction. Additionally, fructose formed in the polyol pathway can also cause metabolic syndrome such as hypertension and nonalcoholic fatty liver disease. Moreover, pseudohypoxia can also lower sirtuin protein contents and induce protein acetylation which can impair protein function. Finally, we discussed the possibility of using nicotinamide riboside, an NAD precursor, as a promising therapeutic agent for restoring NADH/NAD redox balance and for preventing the occurrence of diabetic pseudohypoxia.

**Keywords:** diabetes, fructose, nicotinamide riboside, oxidative stress, poly (ADP ribose) polymerase, polyol pathway, pseudohypoxia, redox imbalance, reductive stress

## Introduction

The concept of pseudohypoxia in adult-onset diabetes (so called type 2 diabetes) and its complications was first brought up by Williamson et al in 1993<sup>1</sup> and has since garnered increasing attention in the field of diabetes research.<sup>2-5</sup> Pseudohypoxia can be referred to as a compromised cellular capacity of utilizing oxygen due to decreased levels of nicotinamide adenine dinucleotide (NAD),<sup>6-8</sup> which can cause accumulation of NADH with occurrence of NADH/NAD redox imbalance.<sup>9-11</sup> This redox imbalance initially would cause reductive stress, but would gradually lead to oxidative stress that damages cellular components including proteins, DNA, and lipids.<sup>7</sup> It is this widespread oxidative stress in diabetes that wreaks havoc on cellular glucose metabolic pathways and culminates in cell death and tissue dysfunction.<sup>12-15</sup> In this review, we discuss the major pathways that can perturb NADH/NAD redox imbalance which leads to pseudohypoxia in diabetes and its complications and the consequences of this pseudohypoxia phenomenon. It should be pointed out that in addition to diabetes, occurrence of pseudohypoxia has also been implicated in the pathogenesis of other diseases including cancers.<sup>16-19</sup>

Correspondence: Liang-Jun Yan  
Department of Pharmaceutical Sciences,  
UNT System College of Pharmacy,  
University of North Texas Health Science  
Center, 3500 Camp Bowie Blvd, Fort  
Worth, TX 76107, USA  
Tel +1 817 735 2386  
Fax +1 817 735 2603  
Email liang-jun.yan@unthsc.edu

While there are numerous enzymes in a cell that use NAD/NADH as their cofactors, there are only two well-recognized enzyme systems that can lead to perturbation of NADH/NAD redox imbalance. These are aldose reductase in the polyol pathway<sup>11,20,21</sup> and poly (ADP ribose) polymerases (PARPs).<sup>22,23</sup> Both of which use NAD as their substrate. Therefore, when activated by hyperglycemia, aldose reductase (AR) can drive overproduction of NADH while PARP can drive depletion of NAD.<sup>24</sup>

## Aldose reductase

Under euglycemic conditions, AR remains in its inactive state because there is not enough glucose to activate its catalytic function.<sup>25</sup> Therefore, the physiological significance of this enzyme remain enigmatic. Nonetheless, it has been suggested that AR, under normal physiological conditions, is acting as a detoxifying agent that can degrade lipid peroxidation aldehyde byproducts such as hydroxynonenal and its glutathione conjugates.<sup>26,27</sup> Chemically, AR catalyzes the first and rate-limiting reaction in the polyol pathway (Figure 1),<sup>28</sup> which becomes activated in diabetes due to hyperglycemia and can dispose approximately 30% of the glucose pool in a diabetic patient.<sup>29</sup> AR reduces glucose to sorbitol at the consumption of nicotinamide adenine dinucleotide phosphate (NADPH). The second reaction of the polyol pathway is oxidation of sorbitol to fructose with concurrent formation of NADH (Figure 1). Therefore, the products of the polyol pathway are sorbitol as an intermediate, fructose and NADH as final products. All three products have been demonstrated to accumulate in diabetic tissues.<sup>30–32</sup> The detrimental role of aldose reductase has been confirmed in AR deletion studies whereby AR deficiency prevents development of diabetes.<sup>33</sup> Likewise, AR gene knockdown has also been shown to slow down the development and progression of

diabetes complications.<sup>34</sup> In fact, many drugs have been designed to inhibit AR for diabetes therapeutic purposes.<sup>35–38</sup>

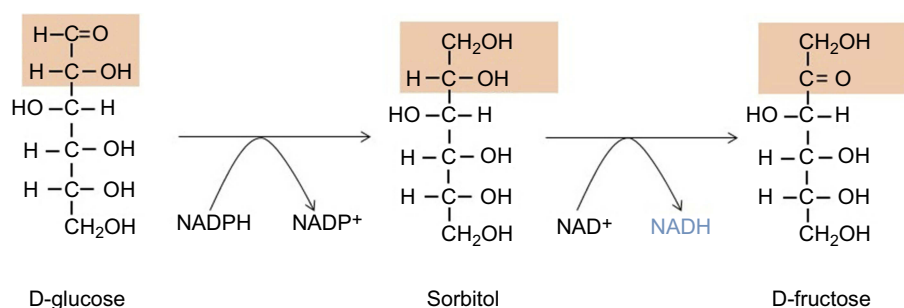
## Poly (ADP ribose) polymerases (PARPs)

PARPs can also be activated in diabetes due to oxidative damage to DNA.<sup>39–41</sup> This family of enzymes uses NAD as its substrate by putting multiple ADP molecules onto target proteins with concurrent release of nicotinamide (Figure 2). While the function of activated PARP is to repair damaged DNA,<sup>42,43</sup> the enzyme can be over-activated in diabetes, thereby leading to NAD depletion and eventual cell death.<sup>22</sup> For example, in our laboratory, we have found that in diabetic lung and pancreas, PARP1 expression is elevated with concurrent decrease in NAD content.<sup>44,45</sup> The detrimental role of PARPs in diabetes has also been confirmed by gene knockout studies whereby mouse lacks functional PARP1 does not develop diabetes.<sup>46</sup> Similarly, PARP deficiency has also been shown to prevent diabetic development and progression.<sup>47</sup> As is the case for AR, PARP has also been explored as a drug target for battling diabetes.<sup>48–51</sup> A recent comprehensive review on PARP mechanism and regulation as well as its potential therapeutic applications can be found in an article authored by Alemasova and Lavrik.<sup>52</sup>

## Consequences of pseudohypoxia in diabetes

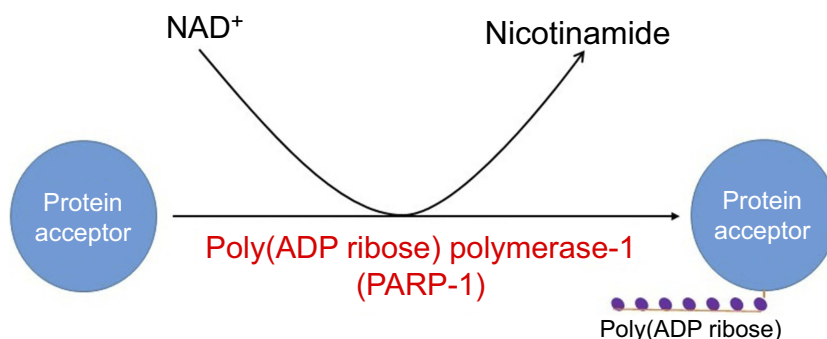
### Reductive stress

The immediate consequence of pseudohypoxia due to NADH/NAD redox imbalance is reductive stress.<sup>7,53</sup> NADH accumulation can give rise to pseudohypoxia and feedback-inhibit many metabolic enzymes or pathways



**Figure 1** The polyol pathway catalyzing conversion of glucose to fructose. This pathway has two reactions; the first reaction involves aldose reductase that catalyzes the conversion of glucose to sorbitol; the second reaction involves sorbitol dehydrogenase that catalyzes conversion of sorbitol to fructose with concurrent formation of NADH.

**Abbreviation:** NADH, nicotinamide adenine dinucleotide.



**Figure 2** Poly (ADP ribose) polymerization reaction catalyzed by poly (ADP ribose) polymerase. Shown is PARP1 as an example.

**Abbreviations:** NADH, nicotinamide adenine dinucleotide; PARP, poly (ADP ribose) polymerase.

such as the glycolytic pathway, pyruvate dehydrogenase complex, Krebs cycle, and the electron transport chain. Indeed, it has been reported that redox imbalance can increase aerobic glycolysis<sup>54,55</sup> and reductive stress can impair brain blood barrier function and endothelial cell angiogenesis.<sup>56,57</sup> Importantly, feedback inhibition of metabolic pathways would further prevent NAD from accepting electrons and accentuate NADH/NAD redox imbalance.<sup>7</sup> Moreover, accumulation of NADH could be linked to increase in GSH and NADPH, which could further aggravate reductive stress,<sup>58–62</sup> leading to cellular dysfunction and cell death.<sup>63,64</sup> It should be noted here that accumulation of NADPH can also contribute to disease development. For example, abrogation of NADH oxidase activity can induce accumulation of NADPH and trigger reductive stress, leading to sensitization of the heart to ischemic/reperfusion injury.<sup>58</sup>

## Oxidative stress

As implicated above, pseudohypoxia is a pathophysiological condition whereby the absolute concentration of cellular NAD is significantly decreased when compared to normal conditions.<sup>1</sup> Therefore, the flip side of pseudohypoxia is increased levels of cellular NADH, which would overload mitochondrial electron transport chain. In other words, pseudohypoxia due to NADH/NAD redox imbalance can overload mitochondrial electron transport chain, leading to excess production of reactive oxygen species (ROS).<sup>7</sup> In particular, as complex I (NADH-ubiquinone oxidoreductase) is the major site in mitochondria responsible for NAD regeneration, complex I overload of NADH can lead to over-production of ROS because of increased electron leakage from the electron transport chain.<sup>65,66</sup> Indeed, our laboratory has found that mitochondrial complex I becomes hyperactive in the diabetic pancreas and

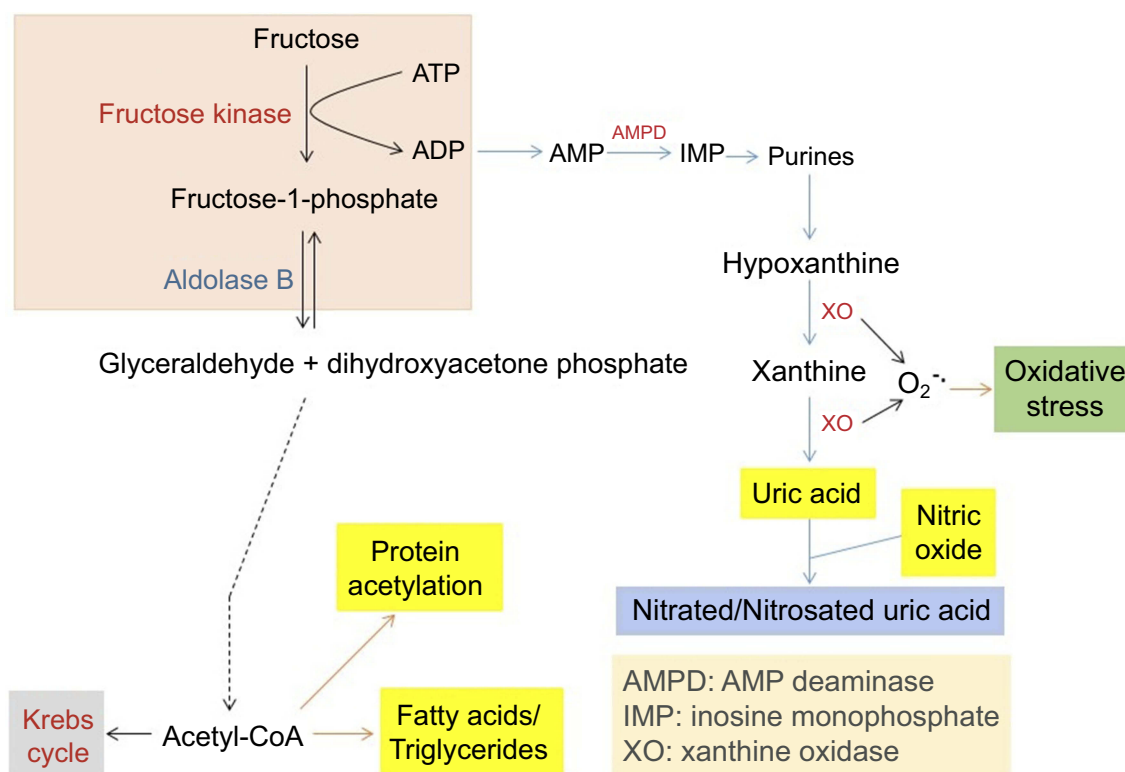
lung due to NADH overloading and this hyperactivity is associated with increased ROS production, decreased ATP synthesis, and increased cell death.<sup>44,45</sup>

## Detrimental effects of fructose

Endogenous production of fructose by the polyol pathway can lead to a variety of metabolic abnormalities.<sup>67,68</sup> As fructose breakdown bypasses the regulation of the glycolytic pathway (Figure 3),<sup>68,69</sup> fructose metabolism can potentially deplete cellular ATP content,<sup>70</sup> which can lead to accumulation of uric acid and development of gout and hypertension.<sup>71</sup> Moreover, as fructose metabolism leads to overgeneration of acetyl-CoA, more lipids can be made in the liver. This can cause increased protein modification such as glycation and acetylation<sup>72</sup> and non-alcohol fatty liver disease that further derange glucose metabolism.<sup>73–76</sup> Therefore, detrimental effect of fructose accumulation and metabolism is another consequence of pseudohypoxia that results from the activation of AR in the polyol pathway.

## Decreased levels of sirtuins

It is well established in experimental conditions that sirtuin protein expression is positively correlated with cellular NAD content. For example, in obese mouse, Sirt3 expression is decreased because of a decreased NAD content<sup>77</sup> while caloric restriction increases Sirt3 expression due to an increased NAD content.<sup>78</sup> Therefore, when NAD becomes scarce in diabetes due to NADH overproduction, sirtuin protein contents are decreased.<sup>79,80</sup> Several members of the sirtuin family are protein deacetylases.<sup>81,82</sup> Therefore, dysfunction of sirtuin proteins can cause over-coating of proteins with acetyl groups.<sup>83</sup> For example, mitochondrial sirtuin 3 (sirt3) expression was lower in diabetic lung than in healthy controls with concurrent



**Figure 3** Pathways of fructose metabolism and detrimental consequences. Major abnormalities resulting from fructose metabolism are shown in the graph, which include potential ATP depletion, accumulation of uric acid that gives rise to gout and hypertension, and nonalcoholic fatty liver disease as well as increased protein acetylation.

increase in protein acetylation.<sup>45</sup> Hence, decreased levels of sirt3 would cause accumulation of acetylated proteins, thereby impairing protein function and derailing metabolic pathways. Conversely, stimulating sirtuin expression or overexpression may serve as approaches to fighting diabetes.<sup>84,85</sup>

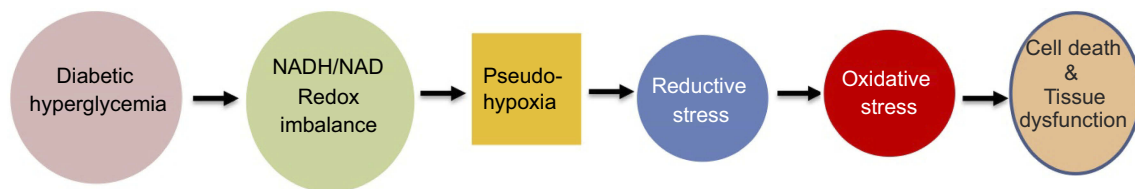
## Eliminating pseudohypoxia by restoring NADH/NAD redox balance

While many steps in NAD metabolism can be potentially explored to restore NADH/NAD redox balance in diabetes, supplementation of NAD precursors has been shown to be another promising approach in battling disease or diabetes.<sup>86,87</sup> One such precursor that is worth mentioning is nicotinamide riboside (NR).<sup>88</sup> This compound is more tolerable<sup>89</sup> and has been tested in a variety of experimental systems.<sup>88,90,91</sup> For example, NR administration in diabetic mouse decreased fasting and nonfasting glucose levels, decreased weight gain, and lessened hepatic steatosis with concurrent protection against diabetic neuropathy.<sup>92</sup> In prediabetic mouse, NR could

improve glucose tolerance, decrease body weight gain, prevent liver damage, and retard the development of liver steatosis.<sup>92</sup> Moreover, NR supplementation was found to increase NAD levels in tissues and to activate sirt3, thereby improving oxidative metabolism and protecting against metabolic dysfunction induced by high fat diet.<sup>89</sup> This study clearly demonstrates that NR supplementation can restore NADH/NAD redox balance by increasing cellular and tissue NAD contents.<sup>89</sup> It should also be pointed out that as NAD can be synthesized de novo from either aspartic acid in bacteria or tryptophan in animals,<sup>93,94</sup> the supplement of these substrates and enhancement of the pertinent enzymes involved in NAD synthesis can also be explored to fight pseudohypoxia in diabetes by boosting NAD content.<sup>95–98</sup>

## Conclusion

The occurrence of pseudohypoxia in diabetes and its complications is caused by NADH/NAD redox imbalance, which is mainly caused by activation of AR in the polyol pathway and PARPs. Pseudohypoxia can induce reductive stress followed by oxidative stress which eventually leads



**Figure 4** Scheme showing the summary of hyperglycemia-induced redox imbalance, pseudohypoxia, reductive stress, and oxidative stress. The eventual events are cell death and tissue dysfunction.

to cell death and tissue dysfunction (Figure 4). As a means of restoring NADH/NAD redox balance and preventing the occurrence of pseudohypoxia, NR has been shown to be a promising compound as a therapeutic agent for diabetes and its complications. It should be noted that other systems such as mitochondrial complex I may also be explored as a therapeutic target for restoring NADH/NAD redox balance to prevent the occurrence of pseudohypoxia in type 2 diabetes.

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## Disclosure

The authors report no conflicts of interest in this work.

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