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Review Article

Biochemistry Section

Implications of Nicotinamide Adenine Dinucleotide Reductive Stress in Health and Diseases- A Narrative Review

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ABSTRACT

Nicotinamide Adenine Dinucleotide (NAD^+) takes part in cellular energy metabolism by accepting hydride equivalents to form reduced NADH, which furnishes reducing equivalents to mitochondrial Electron Transport Chain (ETC). Usually, NADH (H for hydrogen)/NAD^+, redox couple is crucial for cellular redox homeostasis and healthy physiological condition. Reductive Stress (RS) denotes a stable alteration of redox homeostasis due to overexpression of the antioxidant enzyme system, which could deplete Reactive Oxygen Species (ROS). This might potentially switch the redox couple from an oxidative state to a reduced state. Notably, it navigates the cell to RS. Emerging evidence recommends that RS might be even more detrimental than its counterpart oxidative stress. Contemporary perception on fundamental mechanisms of RS, due to perturbation of redox couple, is limited. This review is based on recent comprehension on the biochemical and metabolic role of NADH/NAD^+ redox couple and its title role in promoting diseases like cancer, cardiovascular disease, Diabetes Mellitus (DM), neurodegenerative diseases. Besides, insight into the evolution of NAD^+ redox signaling will augment the perspective on cellular redox homeostasis. Upcoming coveted analyses are desired to establish and explore metabolic transformation to RS. Moreover, the antireductant approach to hinder RS will be noteworthy.

Keywords: Cancer, Electron transport chain, Reactive oxygen species, Redox couple, Redox homeostasis

INTRODUCTION

Redox reactions (oxidation and reduction) represent the transfer of electrons from an electron donor (reducing agent) to an electron acceptor (oxidising agent). Cellular pro-oxidants like Reactive Oxygen Species (ROS), Reactive Nitrogen Species (RNS), and their removal by antioxidants determine the cellular redox domain [1]. Under physiological conditions, ATP generation depends on a series of redox reactions. Notably, redox couples like NAD^+/reduced NAD^+ (NADH), phosphorylated NAD^+ ($NADP^+$)/reduced $NADP^+$ (NADPH) are paramount for cellular redox environment and are responsible for cellular energetics [2]. More so, they play a crucial role in maintaining cellular redox homeostasis, which accounts for a healthy physiological steady state [3]. Redox homeostasis might be a controlling link between the cell cycle and metabolic proceedings [4]. As redox couples are linked to cellular redox environments with cellular energetics, any perturbation in these ratios might lead to detrimental pathophysiological events.

The notion of Reductive Stress (RS) denotes a stable alteration of redox homeostasis. This is introduced in a biological context to describe a sustained increase in reducing equivalents due to overexpression of antioxidant enzyme system that could reposition the redox couples (NADH/NAD^+, NADPH/$NADP^+$) from an oxidative state to a reduced state [5]. Emerging evidence establish that RS might be even more detrimental than its counterpart oxidative stress [1,4,5]. Importantly, RS is seen as an underlying mechanism in the majority of reports on pathological conditions like cancer, cardiovascular disease, neurodegenerative disease, muscular dystrophy, metabolic syndrome, and disorders of mitochondrial Electron Transport Chain (ETC) [5,6]. An in-depth analysis suggests the following mechanisms contributing to pathogenesis: i) regulation of cellular signalling pathway; ii) modification of transcription factors; iii) alteration in the formation of disulphide bonds in the membrane and secretory proteins resulting in activation of unfolded protein and endoplasmic reticulum stress; iv) mitochondrial dysfunction; v) alteration of cellular metabolism [1,5]. It is also speculated that experimental control on cellular antioxidant pathways to manipulate redox control of cell cycle could impede deleterious cellular proliferation [4]. RS also supports the mechanism that could be considered as a beneficial geroprotective approach. Contemporary perception of the fundamental mechanism of RS and its effect on cell metabolism is limited. This article reviews and delineates the metabolic source of the cellular redox network and cellular distribution of the aforementioned redox couple. Also, it focuses on the harmful effect of increased ROS which mediates cellular dysfunction via prolonged RS. Also, it confers an overview of the current state of knowledge on RS and associated chronic diseases. This review is based on a search of Medline, and citation lists of relevant publications in English.

Redox Homeostasis and Redox Stress in Human Beings

Cellular redox environment always maintains uniformity between synthesis of ROS, RNS, and their obliteration by antioxidant enzyme system [7]. ROS are predominantly generated by enzymatic reactions like NAD(P)H oxidase, nitric oxide synthase, xanthine oxidase, or by mitochondrial ETC as functional by-products, which mostly constitute cellular pro-oxidants [Table/Fig-1] [8]. In this context, it should be noted that pro-oxidants are highly reactive in redox reactions, and their physiological role is not confined locally, though their production is compartment specific.

Overall, it can be hypothesised that the redox cycle acts as controlling nexus between oxidative metabolic affaire and cell cycle chores. It has also been demonstrated that ROS takes part in an evaluative contribution in many pathological processes, especially on cell cycle control [4]. It is well-known that ROS can damage protein, lipid, DNA, thus altering the organisms structure and function. It is noteworthy to state that cellular redox homeostasis is perpetuated by a subtle equilibrium between pro-oxidant and antioxidant. Thus, excess oxidant level leads the way to oxidative stress, which is detrimental to cell cycle function and this entails the initiation of many chronic diseases like Cardiovascular Disease (CVD), neurodegenerative disease, ageing and cancer [5]. It is worth mentioning here that several antioxidant trials to impede chronic diseases like cancer and

Free radical	Example	Source
ROS	Superoxide O_2	Endogenous: Aerobic respiration
		Peroxisomal beta-oxidation of fatty acid
	Hydrogen peroxide H_2O_2	Microsomal Cyt P^{450} metabolism
		Phagocytosis by pathogen
	Hydroxyl ion OH-	Exogenous: Exposure to pollution
		Exotoxin- heavy metal, anticancer drug
	Peroxyl ion RO_2-	Anaesthesia, analgesics
		Dietary- excess sugar, saturated fatty acid
RNS	Nitric oxide NO-	L-arginine by NOS
	Nitrogen dioxide NO_2	L-arginine by NOS
	Nitrosyl ion	Nitric oxide reactions
	Peroxynitrite ONOO-	Nitric oxide reactions

[Table/Fig-1]: Sources of ROS and RNS [8].
ROS- Reactive oxygen species; RNS- Reactive nitrogen species

Cardiovascular Disease (CVD) has been debatable [9]. Besides, it has also been reported that antioxidants should be selected based on their availability and ease of delivery [10].

Reductive Stress (RS)

This upcoming hypothesis broadens our understanding of the cellular redox environment. The term RS, not a well-characterised hypothesis, was first reported by Gores GJ et al., during his experiment in rats to induce chemical hypoxia [11]. Usually, under physiological conditions, redox homeostasis is maintained by redox couples such as NADH/NAD^+, NADPH/$NADP^+$ [7]. Besides, this has been revealed that surplus reducing equivalents like NADH and NADPH underscore a close link to RS [5]. Like oxidative stress, RS also backs pro-oxidant production which might cause oxidative damage to cells that can put the cell in distress. In the context of this review, RS is defined as a condition when the equilibrium between pro-oxidant and antioxidant is detrimentally disturbed [12]. This highlights to be deleterious through multiple mechanisms such as elicitation of ROS production, interference in signalling function of ROS, alteration in cell metabolism, curbing of protein disulphide genesis [13].

Consistent with these observations, it is suggested that the cellular redox environment changes during the cell cycle, which also regulates progression from one cell cycle phase to another [14]. Innovative research by Kalen AL et al., focussing on the influence of Superoxide Dismutase (SOD) on redox stress and cell cycle checkpoint, reinforces the redox regulation of cell cycle progression [15]. In addition to this, research evidence also justifies the role of redox regulations in cell cycle proteins, such as Cyclin-Dependent Kinase (CDK) interacting protein (p 21), Rb protein for a G1 checkpoint, cyclin D1, CDK 4-6 [16]. Likewise, another study by Sakamaki T et al., provides strong evidence for the association between the cellular redox domain and cyclin D1 protein, which largely regulates the progression of the cell cycle from G0/G1 to S phase [17]. Importantly, the literature discussed in this section distinctly defends the hypothesis of periodicity in cellular redox nature, which is sustained by intricate uniformity between pro-oxidant and antioxidants. On a similar note, it could also be speculated that restriction of redox homeostasis may repress numerous expressions of such proliferative disorders.

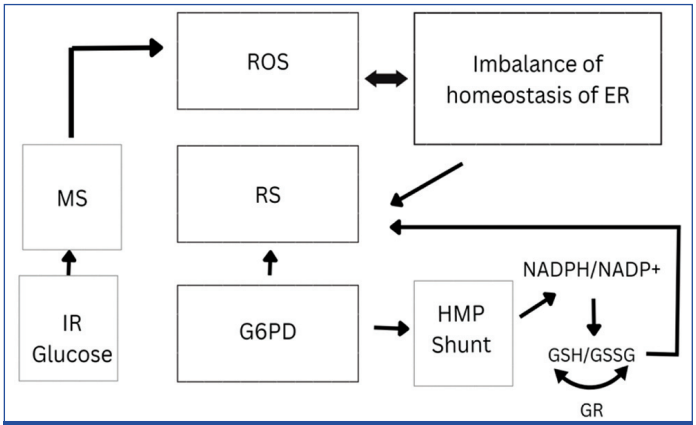
Metabolic Source and Cellular Distribution of Redox Couple

This is already understood that reducing equivalents like NADH and NADPH are indispensable for cellular redox homeostasis. Nonetheless, the term RS could be correlated to the uncurbed magnitude of the aforementioned reducing equivalents. On a cellular level, the companionship of growing reducing equivalents and dearth of useful ROS could impede growth factor-mediated signalling and could elevate mitochondrial dysfunction. Under these circumstances, there is a decreased cellular function and cell survival due to RS [12]. Thus, it is hypothesised that RS could be detrimental to cells and could be associated with several disease processes, such as CVD, neurodegenerative disease, and carcinoma [4].

Metabolic Sources of NAD^+ and $NADP^+$

NAD^+ is a co-factor for several enzymes which catalyse various crucial metabolic reactions. Three major sources for synthesis of NAD^+ are *de novo* synthesis (tryptophan precursor), Preiss-Handler Pathway (nicotinic acid precursor), and salvage pathway (nicotinamide riboside precursor) [3,5]. NAD^+ kinase enzyme converts NAD^+ to $NADP^+$, whereas dehydrogenase enzyme converts NAD^+ and $NADP^+$ to NADH and NADPH, respectively. In this context, the term redox stress refers to the relative paucity of ROS in comparison to NAD^+/NADH redox couples [5]. Metabolic role of redox couples, reducing equivalents, antioxidant enzymes and pathologies leading to imbalance in redox homeostasis, thus denote RS.

The involvement of reducing equivalents and antioxidant enzymes are summarised in [Table/Fig-2] [1]. On a similar note, the interconversion of $NAD(P)^+$ to NAD(P)H highlights the significance of redox balance. Few major carbohydrate metabolic pathways like glycolysis, TCA cycle, Hexose Monophosphate (HMP) shunt, etc., settle the interconversion [18]. In addition, a few other enzymes like alcohol dehydrogenase and aldehyde dehydrogenase also contribute to the formation of NADH. It should be noted here that malate/aspartate shuttle is responsible for compartmental exchange which sustains high cytosolic NAD^+ and high mitochondrial NADH. Any disturbance in the shuttle mechanism might affect redox homeostasis [19].

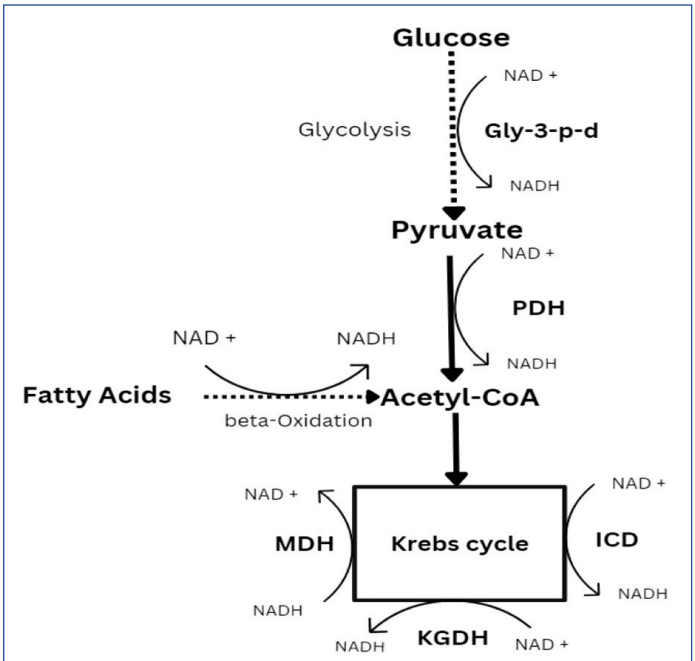


[Table/Fig-2]: Reductive Stress (RS) owing to reducing equivalents and antioxidant enzyme [1].
ROS: Reactive oxygen species; ER: Endoplasmic reticulum; MS: Metabolic syndrome; RS: Reductive stress; G6PD: Glucose 6-phosphate dehydrogenase; IR: Insulin resistance; HMP shunt: Hexose monophosphate shunt; NADP; NAD phosphate; GSH/GSSG; Reduced/oxidised glutathione; GR: Glutathione reductase

Metabolic Source of NADH and NADPH

NADH is primarily generated from interconversion of NAD^+ mediated by enzyme glyceraldehyde -3-phosphate dehydrogenase and lactate dehydrogenase. In addition, a few other enzymes like alcohol dehydrogenase and aldehyde dehydrogenase also contribute to the formation of NADH [13]. As illustrated in the glycolysis pathway, glyceraldehyde-3-phosphate is converted to 1,3 bisphosphoglycerate along with the interconversion of NAD^+/NADH couple. In the same pathway, pyruvate is reduced to lactate, along with the oxidation of NADH to NAD^+. Oxidative decarboxylation of pyruvate to acetyl-CoA also produces NADH. Acetyl-CoA then enters into the Tricarboxylic Acid (TCA) cycle, where NADH is also generated with enzymes Isocitrate Dehydrogenase (ICD), α Ketoglutarate Dehydrogenase (αKGDH), and Malate Dehydrogenase (MDH) [5]. Of note, enzymes like Pyruvate Dehydrogenase (PDH), Glutamate

Dehydrogenase (GDH), ICD, α KGDH, MDH, etc., furnish NADH in the mitochondrial matrix [Table/Fig-3] [5,20]. The aerobic condition can bring about eight NADH molecules when one glucose molecule enters through the TCA cycle.



[Table/Fig-3]: Mitochondrial and cytosolic sources of NADH.
Gly-3-p-d– glyceraldehyde 3 phosphate dehydrogenase, NAD- nicotinamide adenine dinucleotide, PDH- pyruvate dehydrogenase, MDH- malate dehydrogenase, ICD, αKGDH- Alpha ketoglutarate dehydrogenase

Glucose-6-phosphate dehydrogenase and 6-phospho gluconolactone dehydrogenase enzyme (HMP Shunt), are primarily responsible for the generation of cytosolic NADPH [5]. Other sources of cytosolic NADPH include ICD, Methylenetetrahydrofolate Reductase (MTHFR), Formyl Tetrahydrofolate Dehydrogenase (FTHFDH) [21]. In addition, malate to pyruvate decarboxylation by malic enzyme, usually coupled with the conversion of $NADP^+$ to NADPH. Considerable origin of mitochondrial NADPH is mitochondrial enzymes such as ICD, Malic enzyme, Methylenetetrahydrofolate Dehydrogenase (MTHFD), FTHFDH [5]. In addition, Nicotinamide Nucleotide Transhydrogenase (NNT) also contributes to the mitochondrial NADPH pool [4].

The literature presented in this review stands up for the concept that disruption in redox control could usher in various disease pathologies. As the centre of attention of this review is RS induced by a change in redox potential, current findings on various RS-associated chronic diseases like cancer, CVD, diabetes, neurodegenerative disease will be presented below.

Role of Reductive Stress (RS) in Cancer

There is growing appreciation to acknowledge the contribution of RS in cancer development, advancement, and curative approach. As an emerging concept, RS has been identified as a major contributor to carcinogenesis [22]. As discussed previously, redox homeostasis is not only vital for the maintenance of normal physiological processes but also important for cell growth and survival. Moreover, perturbation in redox balance is definitely involved in the proliferation and progression of cancer. It is stated before that surplus reducing equivalents can be linked to RS. This in turn can disturb cell signalling pathways and mitochondrial homeostasis. In this context, it is important to understand that antioxidants influence RS in tumour microenvironment. RS, antioxidant enzymes, and disturbed homeostasis are incongruously link to excess ROS production [22].

On a similar note, cancer cells could amend to more reductive conditions and a reductive environment motivates the proliferation of cancerous cells. It is noteworthy to mention here that nuclear factor erythroid 2-related factor 2 (Nrf2), a transcription factor, may act as a master regulator of cellular redox balance [23]. Importantly, this has been identified to promote RS and might contribute to altered metabolism and the development of carcinogenesis. Moreover, it has been speculated that tumour cells expropriate Nrf2 signal which facilitates cancer cell survival even with resistance to anticancer agents [24]. Thus, activation of Nrf2 may give a new impetus to cancer metastasis. It is noteworthy that recent studies have addressed the involvement of divergent activity of Nrf2 in several types of cancers such as lungs, breast, ovary, etc., [25].

Moreover, concurrent usage of chemotherapy and antioxidants leads to the diminished biological activity of alkylating chemotherapeutics through the induction of antioxidant enzymes [26]. As stated before, that metabolic alteration and adaptability are signatory characteristics of cancer. Of note, this could affect cellular redox homeostasis, which ultimately is linked to resistance to chemotherapeutics [27]. In general, there occurs metabolic alterations and excess ROS in cancer cells [28]. RS is utilised to achieve therapeutic resistance which is favourable for tumour growth and metastasis. For instance, a recent study by Metere A et al., on thyroid cancer tissue signifies metabolic reprogramming (decrease TCA cycle and enhance glycolysis), which indicates their progress and endurance [29]. Several inquiries stand unsettled regarding the detrimental and defensive consequences of ROS on cell physiology.

Role of Reductive Stress (RS) in Cardiovascular Disease

It is now clearly recognised that intracellular redox balance could be preserved by a mechanism that regulates production (pro-oxidants) and removal (antioxidants) of ROS. Of note, mitochondria (ETC by-products) and extramitochondrial (enzymes such as NAD phosphate (NADPH) oxidases) are the two major sources of ROS generation in the heart [30]. As explained earlier, the redox environment is defined by NADH, NADPH, and their respective oxidised form. Emerging suggestions specify that RS is assumed to be more deleterious than its counterpart oxidative stress by a mechanism where the saviour turns predator [31]. As explained earlier in this review, RS is defined by a sustained increase in reducing equivalents due to overexpression of antioxidant enzyme system, that could reposition the redox couples from an oxidative state to a reduced state. It is now widely recognised that RS alters redox potential which may promote cardiovascular deterioration such as myocardial ischaemia-reperfusion injury, cardiac hypertrophy, cardiomyopathy, heart failure, and mitochondrial dysfunction [32]. A noteworthy question here is that how both oxidative stress and RS usher to matching consequences. Many queries remain unresolved about the defensive and detrimental effect of RS on CVD.

It is already known that fibrous plaque and atherosclerosis have been identified to play a crucial part in Coronary Heart Disease (CHD). Data suggest that vascular smooth muscle cell proliferation could initiate ROS generation and abundant expression of ROS signalling can further activate cellular proliferation during atherosclerosis [33]. Based on this report, it has been elucidated that intracellular ROS is substantially involved in the pathogenesis of CVD. Pyrimidine nucleotide NADH, NADPH plays a major role in the generation of ROS and their removal by the antioxidant enzyme. Importantly, NADPH oxidase, Platelet-Derived Growth Factor (PDGF), xanthine oxidase, and phagocyte NADPH oxidase mostly contribute to ROS generation in ischaemia [34]. There is growing appreciation that activation of NADPH oxidase (NOx) has a considerable impact on the pathogenesis of CVD [12]. So far, several types of NOx have been reported, out of which NOx4 has been reported to utilise both NADPH and NADH catalytically in cardiac tissue [35]. Handy DE and Loscalzo J shed some light on this enigma, which is considered as a key source of ROS [12]. Several studies on NOx4 have been analysed in the model of cardiac diseases, which explain its role by controlling endothelial Nitric Oxide Synthase (eNOS) expression and NO production on vasculature [36]. Evidence from Touyz RM et al.,

suggests altered expression of NOx4 in atherosclerosis, justifying its response to stress [37]. Looi YH et al., however, suggest that NOx2 is considered to be constitutively active in myocardial infarction [38]. Additionally, a link between NOx4 and Nrf2 activation was shown in cultured endothelial cell experiments. It is truly unclear whether overexpression of endogenous NOx4 will promote redox stress or angiogenic response and cell survival [39]. Many questions remain unanswered about the defensive and detrimental effect of NOx4 on CVD. As RS and NOx, likely play an essential role in redox signalling, yet it is undefined how oxidants bring about a defensive role instead of harmful action.

The concept of protein aggregation cardiomyopathy and cardiac dysfunction is not new. Already it is well-known that αB-crystallin (CryAB), acts as chaperone protein (proper folding or assembly) for cardiac myofibrillar protein desmin and actin. Pathogenesis of cardiomyopathy is associated with misfolding and subsequent cytoplasmic aggregates of desmin [40]. Furthermore, an additional mouse model with overexpression of CryAB displays an increase in NADPH and antioxidant enzyme catalase and glutathione reductase, which supports the concept of RS in cardiac disease. Interestingly, the mitochondrial matrix displays a reduced redox potential to a great extent [41]. Any variation in the redox profile promotes mitochondrial dysfunction and cardiac pathology. It must be mentioned here that mitochondrial redox state is relevant to the heart as it needs a constant supply of ATP via the ETC. Extensive clinical experimental evidence could throw more light on therapeutic means for effective prevention and treatment of various CVD.

Role of Reductive Stress (RS) in Diabetes

The DM has been known since antiquity. India is one of the epicentres of the global diabetes pandemic. Chronic elevation of blood glucose is a characteristic feature of DM. Type 1 DM (IDDM) results from insulin deficiency, whereas type 2 DM (NIDDM) is delineated by insulin insensitivity in peripheral tissues due to Insulin Resistance (IR) [42]. In India, 77 million people were estimated to have diabetes in 2019, and by 2045, that number is projected to reach over 134 million [43].

It is primarily due to interaction between lifestyle, genetic, and environmental factors [44]. Although the exact cause of diabetes is not thoroughly acknowledged, it is postulated that perturbation of cellular redox homeostasis may notably affect the progression of this disease [45]. As hyperglycaemia and IR is a characteristic feature of type 2 DM, hence it would be sufficing to mention that there is an increase in glucose metabolism in such cases. Thus, persistent hyperglycaemia explains more production of NADH for ATP through the glycolysis pathway. Surplus NADH may constitute the framework for redox imbalance between NADH and NAD [46]. Studies have shown that the above redox disproportion is assumed to be the pathogenesis of type 2 DM [45-47]. It has been discussed earlier that there occurs overproduction of NADH in diabetes via conventional glucose metabolic pathway (Glycolysis and Kreb's cycle) as shown in [Table/Fig-3]. Following enzymes can be ascribed for this function such as glyceraldehyde -3-phosphate dehydrogenase in glycolysis, PDH complex in link reaction, ICD in TCA cycle, and MDH in TCA cycle.

Additionally, mitochondrial beta-oxidation of fatty acids plays a conspicuous role in maintaining energy homeostasis by producing NADH. Although fatty acid oxidation acts as a crucial energy source for the heart, skeletal muscle, and kidney, it also provides essential energy in post-absorptive and fasting states [48]. Nonetheless, under hyperglycaemic conditions, NADH is overproduced which might lead to RS in DM. In this context, it is noteworthy that the polyol pathway is enhanced under diabetic hyperglycaemia, which is another source of NADH [49]. This also can contribute to redox imbalance between NADH and NAD.

The study provides evidence that mitochondrial dysfunction and IR in type 2 DM should be linked together [50]. Of note, mitochondria typically have many intermediary metabolites and reducing equivalents as a result of various metabolic reactions in it [51]. This finding suggests that any change in mitochondrial function may bring about anomalous insulin signalling pathways. Ultimately insufficient glucose utilisation augments type 2 DM [52]. Strikingly, these changes can be reversed by aiming to upgrade mitochondrial function, which may contribute to a curative plan of action for IR and DM.

As mentioned earlier that redox equilibrium keeps the cellular homeostasis. RS can occur when there is an unusual increase in reducing equivalents which reposition the redox balance of NADH/NAD^+ to a more reducing state. It is noteworthy, that sirtuins and Poly ADP Ribose Polymerases (PARPs) are the enzymes that can use NAD^+ as their substrate [53]. It should be noted that chronic hyperglycaemia in diabetes is usually accompanied by low sirtuin protein due to low NAD^+ (excess NADH). It has been hypothesised that a high sirtuin level can promote redox balance in diabetes, which could amend diabetes and future complications [54]. Similarly, PARP, which is reported to be overactivated in diabetes, may attenuate NAD^+ causing redox imbalance [55]. Hence, it is imaginable that restoring redox balance by PARP inhibitor should be a promising approach for anti-diabetic therapy. Additionally, NAD^+ analog can also restore NADH/NAD^+ redox balance in diabetes. Future intensive studies on restoring redox balance can be helpful for antidiabetic therapeutic strategies.

Role of RS in Neurodegenerative Diseases

Neurodegenerative disorders are delineated by cumulative loss of selective neurons of the brain and spinal cord, for example, superior temporal sulcus in Alzheimer's disease and substantia nigra in Parkinson's disease [56]. The exact cause behind the pathology of these diseases remains unclear. Several studies provide compelling evidence in support of inflammation-causing protein aggregation and subsequent alteration in neurotransmitters [1,57]. There are still many questions to be answered regarding RS participation in neurodegenerative diseases. An animal study by Lloret A et al., showed that RS is the emerging cause of Alzheimer's disease even before the onset of the disease [57]. The cause of RS could be related to a high level of G6PD and GSH, which may be crucial for maintaining the mitochondrial membrane sulfhydryl group. Likewise, overexpression of antioxidant enzymes may trigger the risk of Alzheimer's disease by impairing redox homeostasis [1].

Future studies are necessitated to analyse how RS influences cell metabolism and how cells adapt to such stress and how the biological consequence of imbalanced redox niche is responsible for causing Alzheimer's disease. Similarly, Parkinson's disease is a common neurodegenerative disease that involves gradual deprivation of dopaminergic neurons with an unusual increase in alpha-synuclein in the substantia nigra. Although aetiology remains elusive, ROS-mediated damage has been implicated to be involved in the development of the disease. The Rotenone Model of Parkinson's disease by Greenamyre JT et al., showed significant augmentation of NADH/NAD^+ in association with the disease [58]. It is important to note that mitochondrial dysfunction and neuroinflammation have been attributed to redox cellular equilibrium in substantia nigra, which predicts the progression of the disease [59]. Clinical trials in a large population will cover the knowledge on the potential role of antioxidants and their impact on living beings.

CONCLUSION(S)

Despite the contemporary conviction that oxidative stress is a significant player for underlying disease processes, there is extending acknowledgement that RS is even more harmful to the

biological system. It is the ultimate time to review and reconsider the importance of a nebulous balance between oxidative stress and RS in health and disease. On a cellular level, the NADH/NAD^+ redox couple maintains and harmonises cellular metabolism and is so assumed to be responsible for a healthy physiological steady state. Sustained and perpetual augmentation of reducing equivalents could shift the redox couples more towards a reduced state, which has been linked to pathological disorders. This review article highlights the metabolic sources of the redox couple and also confabulates current knowledge on RS and associated chronic diseases. Several recent literature searches have proclaimed that cancer, DM, and many CVDs are redox imbalance diseases. This review article reasonably stands up for redox paragon which promotes origination of reducing equivalents and accompanying RS. Despite extended research works, several queries stand still unsettled regarding the detrimental and defensive consequences of ROS, antioxidant defence mechanisms on cell physiology. Consistent with the knowledge reviewed here, it is suggested that targeted antioxidant therapy could mend the redox homeostasis and its impact on living beings.

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