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8-Hydroxy-2'-Deoxyguanosine (8-OH-2dG) as a Biomarker of Oxidative Stress (OS) in the Acute Exacerbation of Spontaneous Preterm Birth (SPTB)

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Abstract

Spontaneous preterm birth (SPTB) is characterized by the delivery of a baby before 37 completed weeks of gestation, and this condition is associated with significant health challenges for the newborn. Emerging evidence highlights the importance of biomarkers for understanding the mechanisms underlying SPTB. One such biomarker, 8-OH-2dG, plays a critical role in evaluating oxidative stress and its impact on pregnancy outcomes. It has been demonstrated that 8-OH-2dG is a product of oxidative DNA damage and is widely recognized as a key indicator of cellular oxidative stress. Elevated reactive oxygen species in SPTB result in higher levels of the DNA degradation product 8-OH-2dG in amniotic fluid, causing damage to maternal and fetal tissues that could lead to premature rupture of fetal membranes. Therefore, evaluating the role of 8-OH-2dG in SPTB is of great interest. This review provides an overview of the current knowledge on 8-OH-2dG as a biomarker for SPTB and aims to elucidate its mechanism in this condition.

Keywords

Preterm Birth, 8-Hydroxy-2'-Deoxyguanosine, Oxidative Stress, DNA Damage

1. Introduction

SPTB is the most common cause of neonatal mobility and mortality worldwide. SPTB is associated with various risk factors, including oxidative stress, infections, medical and obstetrics complications, a history of preterm birth, advanced maternal

age lifestyle factors, and genetic predispositions [1]. SPTB is typically diagnosed based on gestational age, determined either by the last menstrual period or ultrasound when no additional factors suggest an alternative cause of early delivery [2]. The global prevalence of SPTB is estimated to range from 10% to 15%, with significant regional and socioeconomic variations. This rate is constantly increasing, primarily due to factors such as rising maternal age, assisted reproductive technologies, and certain lifestyle habits such as smoking and inadequate prenatal care. SPTB is more common in non-Caucasian populations, including African American, Hispanic American, Native American, Pacific Islander and South or East Asian populations [1] [3].

SPTB has been known to be associated with increased risk of neonatal infection, mortality and long-term developmental complications in the offspring. Children born preterm are more predisposed to chronic health conditions such as chronic lung disease, cerebral palsy, metabolic syndrome and cardiovascular disease later in life [4].

Although extensive research has been conducted on the pathophysiology of SPTB, the precise mechanisms of its development remain unclear. Inflammation, disruption of normal placental function and various maternal and fetal stressors are believed to play significant roles [5]. Growing evidence indicates that inflammation, disruption of the uteroplacental signaling pathways, alterations in placental and fetal growth factors and endoplasmic reticulum stress contribute to SPTB. However, oxidative stress (OS) is considered a primary cause of SPTB, and its components should be closely monitored during pregnancy and treatment [6].

Researchers have identified 8-OH-2dG as one of the most important biological markers of OS [7]. Although living cells possess a diverse array of DNA repair mechanisms, their enzymatic repair systems do not always eliminate all DNA modifications. This can lead to serious problems for cells, as the presence of unrepaired DNA can result in mutations, changes to genetic information, mutagenesis, and cell apoptosis [7] [8]. Growing evidence suggests that the accumulation of a substantial number of lesions, particularly 8-OH-2dG, is an important indicator of spontaneous SPTB onset and can lead to long-term health complications for both mothers and their offspring [9].

This review summarizes current knowledge on the impact of 8-OH-2dG on spontaneous SPTB development. Additionally, biomarkers of SPTB and several mechanisms connected with OS induction and SPTB development are reviewed and discussed.

2. Pathways of ROS Production

Reactive oxygen species (ROS) are highly reactive derivatives formed as a result of incomplete oxygen reduction. These species possess high reactivity due to having at least one unpaired electron in their valence shell [10]. Approximately 5% of the total inhaled oxygen is converted into ROS, the most significant being the superoxide radical ($O_2^{\bullet -}$), hydrogen peroxide (H_2O_2), hydroxyl radical ($^{\bullet}OH$) and

singlet oxygen ($1O_2$). ROS are primarily produced in response to radiations (alpha, beta, gamma, X-radiation (X-ray)), ultraviolet-visible (UV-Vis), inflammation (infections), chronic diseases (alcoholism, and cancer), chemical compounds (pesticides, benzopyrene, nitrous oxide), metabolic processes (fatty acid peroxidation) and metabolic disorders (diabetes mellitus) [11]. In addition, ROS are generated from normal physiological processes occurring in various cellular compartments. Under physiological conditions, these processes maintain ROS at appropriate levels and facilitate proper redox reactions in the respiratory chain, oxygen transport by hemoglobin, energy sources regeneration, phagocytosis, gene expression regulation and activation of cytochrome P450 [12].

During fetal development, physiological changes in the chorioamniotic membrane result in ROS emergence. It is widely known that the fetal membranes consist of proteins, lipids and carbohydrates. Consequently, increased ROS can cause damage to proteins by impairing DNA molecules and cell membrane lipids, ultimately leading to premature membrane rupture [13].

ROS are generated in the mitochondrial matrix during the electron transport chain [9]. The mitochondrial structural components include nicotinamide nucleotide dehydrogenase enzymes, complexes 1, 2, 3, and 4. During the electron transport chain, electrons flow through these inner mitochondrial complexes [8] [14]. A Q-cycle occurs between complexes 1 and 3, reserving the electrons passing through these complexes. The Q-cycle contributes to ROS production, as demonstrated in **Figure 1**. Superoxide dismutase interacts with free radicals and converts them into hydrogen peroxide (H_2O_2) [15]. Subsequently, glutathione donates electrons through the action of Glutathione Peroxidase, resulting in oxidized glutathione. To regenerate the reduced glutathione (GSH), NADPH is utilized in the presence of glutathione reductase enzyme. The reduced glutathione is then oxidized to GSSG in the presence of protein thiol reduction [16].

During oxidative stress, mitochondrial enzymes become inactive due to the formation of disulfide bridges. These bonds are disrupted by electrons from 2GSH, leading to a reduction and reactivation, thereby counteracting the effects of oxidative stress [15].

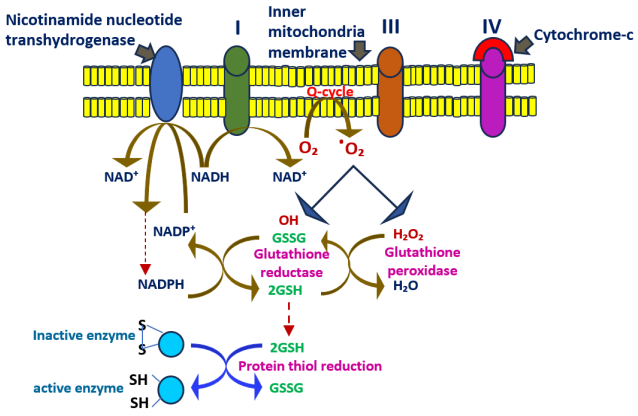

Figure 1. Diagram illustrating the mechanism of action in oxidative stress production.

3. The Role of 8-OH-2dG in SPTB

According to existing literature, elevated ROS levels increase the production of 8-OH-2dG, a biomarker commonly used to assess OS in SPTB [17]. Two mechanisms by which 8-OH-2dG may contribute to SPTB have been identified: weakening of the fetal membrane and induction of an inflammatory response [7] [18].

The 8-OH-2dG can damage fetal membranes by affecting their lipid components. Lipid peroxidation, the oxidative degradation of lipids, leads to electron loss and the formation of peroxyl radicals as intermediates, weakening the membranes [19]. Not all lipids undergo peroxidation; polyunsaturated fatty acids (PUFA) are more susceptible due to their structural characteristics. PUFA contains at least two double bonds, and the methylene bridges between bonds contain two highly reactive hydrogen atoms [20]. When the hydroxyl radicals (•OH) attach to the hydrogen on the methylene bridges, they stabilize in water molecules. Lipid peroxidation typically progresses through three steps: initiation, propagation and termination. The initiation step involves the attack of free radicals on stable lipid molecules, transforming them into free radicals. The propagation step occurs when lipid radicals react with oxygen molecules, forming peroxyl radicals. Termination occurs when two radical species react to form stable molecules [21], as shown in Figure 2. However, before termination, some radicals may have already damaged the cell membranes.

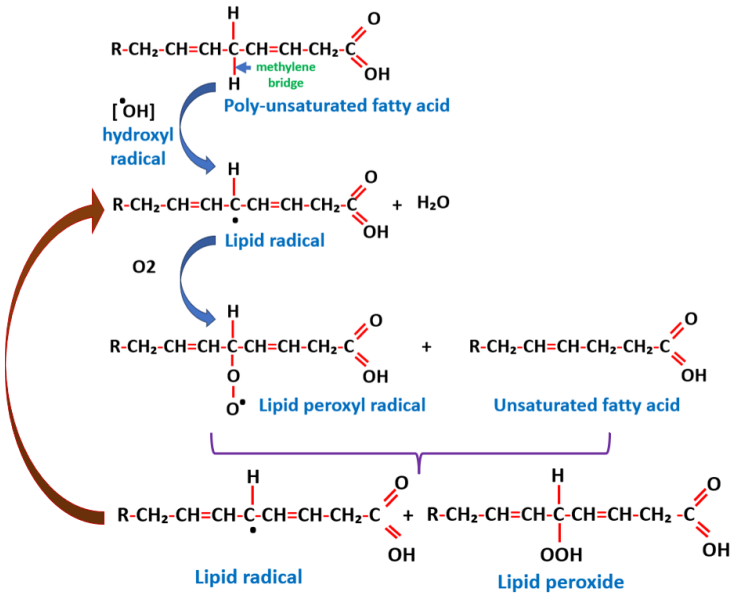

Figure 2. Diagram showing the mechanism of action in lipid peroxidation.

When ROS damages guanosine, it results in the formation of 8-OH-2dG. This compound plays a crucial role in the progression of inflammatory processes, which can subsequently stimulate the production of prostaglandins, which are key mediators in initiating labor [6] [22] [23]. Two intracellular signaling cascades are activated by 8-OH-2dG: the nuclear factor kappa-light-chain-enhancer of activated

B cells (NF-κB) pathway [24] and the nucleotide-leucine-pyrin domain-3 (NLRP3 Inflammasome) pathway [25]. Activation of these pathways results in the transcription of pro-inflammatory genes, including cytokines, essential for initiating and propagating inflammatory responses [26]. Cytokines, in turn, initiate the conversion of arachidonic acid located in the cell membrane phospholipids into prostaglandins via cyclooxygenase enzymes. Prostaglandins are responsible for initiating labor by remodeling the cervix and triggering uterine contractions [27] [28], as shown in Figure 3.

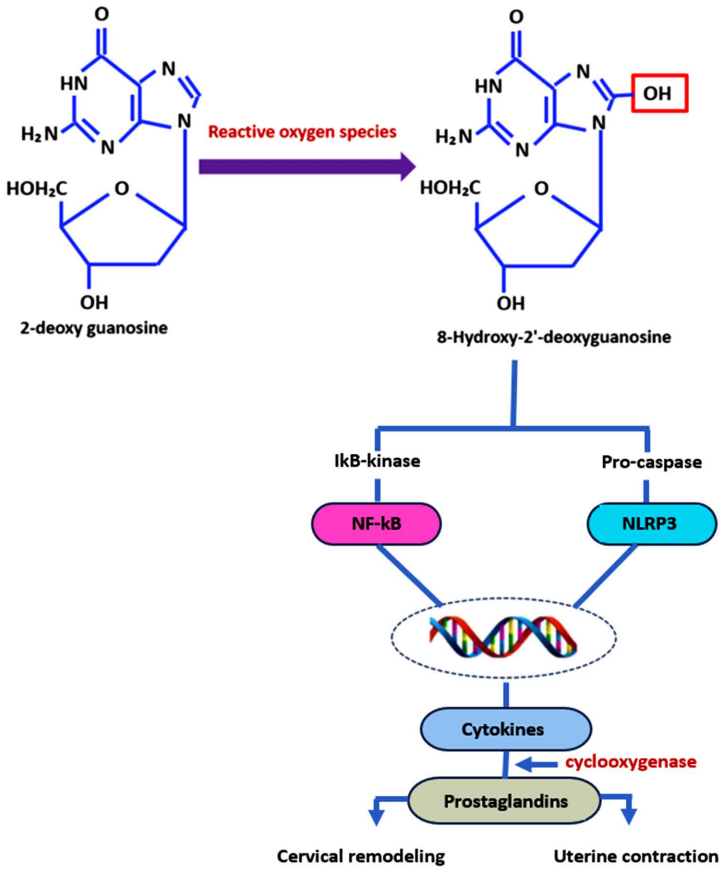

Figure 3. Diagram illustrating the role of 8-OH-2dG in labor induction.

4. Summary

This review communicates complex information about preterm birth and oxidative stress biomarkers in a clear and systematic manner. Emerging evidence highlighted the importance of biomarkers for understanding the mechanisms underlying SPTB. However, future research should focus on expanding our understanding of 8-OH-2dG as a biomarker for SPTB. It is essential to identify high-risk patients and investigate the relationship between 8-OH-2dG levels and SPTB to develop preventative measures. Enhanced comprehension and monitoring of SPTB and 8-OH-2dG levels could contribute to improving preventive strategies for SPTB.

Consent for Publication

Not applicable.

Conflicts of Interest

The author declares no conflicts of interest regarding the publication of this paper.

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