Biochemistry of Hydrogen Peroxide

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Hydrogen Peroxide (H2O2) is the nonionized 2-electron reduction product of unstable molecular oxygen (O2), which plays a central role in maintaining the redox cycle of living cells.

Chemistry	H2O2	oxidative	Free radical	Fenton Reaction
Neurodegener	rative diseas	ses Iron	Hydroxyl rad	ical

1. Introduction

Hydrogen Peroxide (H₂O₂) is a diverse potent oxidizing and inexpensive chemical molecule, which has chemical applications ^[1], biological functions ^[2], and therapeutic applications which include antimicrobial and oxidizing agents ^[3]. Over the last decade, H₂O₂ has been used as a green oxidant and alternate source of oxygen (O₂) to convert biomass to chemical synthesis ^[1]. It also acts as an environmentally friendly oxidizing catalyst in many oxidizing chemical processes because the end product of its decomposition is only a water (H₂O) molecule ^[4]. H₂O₂ is one of the closest cousins of water and is a non-planar molecule having an open book structure. It is also regarded as the smallest chiral molecule, which can undergo a disproportionation reaction to act both as oxidizing and reducing agent ^{[5][6]}.

 H_2O_2 is a strong oxidant, having a reduction potential of 1.76 V at pH 7.0, 25 °C. Therefore, it is more oxidizing than hypochlorous acid (HOCl) or peroxynitrite (ONOO⁻), for which the reduction potentials are 1.48 and 1.4 V, respectively. However, relative to these two reactive species, the reactivity of H_2O_2 is relatively low with various biological molecules like nucleic acid, proteins, and lipids. Further, this can be explained by its higher activation energy barrier, which must be overcome to release its oxidizing power. In other words, the chemical reactions of hydrogen peroxide are kinetically controlled rather than thermodynamically driven ^[Z]. The H_2O_2 produced during cellular metabolism is found to be stable, compared to (HOCl) having a half-life in minutes and (ONOO⁻) having a half-life of 10⁻³ s ^{[B][9]}. It is a major oxidant produced by the activated neutrophils at the site of inflammation from H_2O_2 and chloride, catalyzed by the enzyme myeloperoxidase, a leukocyte-derived enzyme. HOCl exerts its oxidizing power through the oxidation and chlorination of biomolecules like nucleic acids, lipids, and cholesterol ^[10]. It confers its oxidizing power via chlorination of amino acids like tyrosine to form 3-chlorotyrosine and damage the collagen ^[11]. HOCl is more reactive than H_2O_2 (rate constants of 3×10^7 M⁻¹ s⁻¹ and 0.9 M⁻¹ s⁻¹, respectively), however, the redox potential for the 2-electron reduction is larger for the H_2O_2 in forming H_2O , than for the former in releasing chloride ^[12]. ONOO⁻ is formed by the reaction between superoxide radical anion (O_2^{-}) and nitric oxide radical (NO^{*}). It is highly toxic to biomolecules, oxidizes lipids, Met, and tyrosine residues in proteins ^[13]. The nitrotyrosine residues are considered as a marker of $ONOO^-$ induced cellular damage, potentially serving as a "peroxynitrite footprint" in the biological oxidation process. The main biological target of $ONOO^-$ is deoxyribonucleic acid (DNA), where it oxidizes the base pairs, causing nitrative and oxidative DNA lesions such as 8-nitroguanine and 8-oxodeoxyguanosine respectively ^{[14][15]}. Recent evidence has shown that the protein sulphenic acid (SH) significantly reacts faster with $ONOO^-$ compared to H_2O_2 ^{[16][17]}.

H₂O₂ is a weak one-electron oxidant, although the one-electron reduction product, the hydroxyl radical (HO^{*}) is one of nature's most vulnerable bio-reactive species, which can create an oxidizing environment in the living cell and ultimately lead to its death $\frac{[18][19][20]}{18}$. The redox property of H₂O₂ is dependent upon the pH of the solutions, as the pKa of H₂O₂ is 11.6, so it is mostly unionized at physiological pH. The strong nucleophilicity of hydroperoxide nucleophile (-OOH) is limited due to its high pKa. H₂O₂ also acts as electrophile due to the polarization of the peroxide bond (O-O). The homolytic bond dissociation enthalpies of peroxide in H₂O₂ at 298 K is 50 kcal/mol, whereas the heterolytic bond dissociation enthalpies of H₂O₂ is 290 kcal/mol. The unexpected chemical reactivity of hydrogen peroxide is generally attributed to the weakness of (O-O) and therefore, it is homolytically cleaved in presence of heating, radiolysis, photolysis, or transition metals ^[21]. Prof. John O. Edwards, a pioneer in the field of peroxide chemistry, has demonstrated the mechanism of peroxide chemistry exquisitely. According to him, thiolates (-S⁻) are more reactive than (SH). Hence, (-S⁻), being nucleophilic, react with H₂O₂, an electrophile, by bimolecular nucleophilic substitution (SN2) reaction mechanism displacing ⁻OH as leaving group ^[22]. However, recent developments on this mechanism suggest that the by-product of the reaction is H₂O instead of hydroxyl anion (HO^{-}) [23][24]. The nucleophilic reaction of a protein (-S⁻) on electrophilic H₂O₂ forms H₂O as a by-product and results in the formation of cysteine sulphenic acid (CysSOH), the process is also known as S-sulfenylation. Depending upon the protein microenvironment where the thiolate is located, the reaction is exclusive to $(-S^{-})$, and at physiological pH, dependent upon the pKa values of the sulfur-containing amino acids. In addition, hydrogen bonding also plays an important part in the ionization of (SH) to (-S⁻) ^{[25][26][27]}. Further, the SN2 paradigm was also challenged and proved by hybrid quantum-classical (QM-MM) molecular dynamics simulations [26]. The nucleophilicity of H_2O_2 could be explained by the reaction of -OOH with organohalides [28], and oxidation of boron compounds ^[29]. H_2O_2 , a green redox molecule that has properties of both oxidant and reductant, also can be a nucleophile and electrophile in chemical reactions. Having all these characteristics it reacts poorly with most biological molecules because of the high activation energy barrier and the reaction rate is kinetically controlled. Thus, the vigorous oxidizing power of H₂O₂ comes indirectly from its transition metal catalysis into HO[•] by Fenton and Haber-Weiss reactions ^[7]. In addition, Copper/zinc superoxide dismutase (Cu/Zn SOD1), which is a ubiquitous natural antioxidant enzyme, is mainly involved in dismutation of ionizable toxic O2* radical in vivo to produce a non-ionizable less toxic redox molecule H₂O₂, which has the ability to generate HO[•], thereby acting as pro-oxidant in certain disease conditions [30][31].

2. Hydrogen Peroxide as Double Edge Sword in Living Cells

 H_2O_2 acts both as a redox signaling molecule and an oxidative stress molecule. As a signal transduction molecule H_2O_2 has a role in controlling various key cellular processes like cell shape changes, initiating proliferation,

recruitment of immune cells, calcium ion (Ca⁺²) signaling in the lumen of endoplasmic reticulum and mitochondriaassociated membranes ^{[32][33]}. It acts as a secondary messenger in insulin signaling and several growth factorinduced signaling cascades ^[32]. Also, H₂O₂ is involved in the chemical modifications of specific Cys amino acids, which are expressed in some cellular proteins ^[34]. H₂O₂ generated during physiological oxidative stress conditions in the concentration of around (1–10 nM) acts as a redox signaling molecule in various cellular processes creating oxidative eustress, although, the higher or pathological concentration of H₂O₂ of around (>100 nM) is known to cause deleterious effects to cellular biomolecules, this effect is called oxidative distress ^[2]. According to many reports, the higher pathological concentration of H₂O₂ in oxidative stress conditions can go up to 150µM ^{[35][36][37]}.

Various studies have been conducted to examine the concentration at which the H2O2 acts as a cytotoxic and neurotoxic agent. Further, various studies have investigated the mode of cell death caused by H₂O₂, mainly due to apoptosis or necrosis [38][39][40]. It was found that the effects of H₂O₂ are largely dependent upon the mode of cell death induced (apoptosis or necrosis) depending on the cell type used, its physiological state, length of exposure to H_2O_2 , the H_2O_2 concentration used, and the cell culture media employed [38][41]. Yoshiro and colleagues (2006) $^{[42]}$, investigated that 50µM of H₂O₂ exhibited caspase-9 and caspase-3 activation, finally leading to apoptotic cell death in human T-lymphoma Jurkat cells, whereas a higher concentration of 500 µM caused necrotic death. Teramoto and the group (1999) [43], demonstrated that a lower concentration of 10–100 µM predominantly caused apoptosis, however, a higher concentration of 1-10 mM induced necrosis in human lung fibroblasts cells. Troyano and associates (2003)^[44], demonstrated caspase-9 and caspase-3 activation and death by apoptosis in U-937 human promonocytic cells when treated with 200 μ M H₂O₂. Although, treatment with 2 mM H₂O₂ caused necrosis. Gulden and the group (2010) [35], investigated in detail how exposure time and cell concentration affect the cytotoxic potency of H₂O₂ in vitro. They investigated those median cytotoxic concentrations decreased from 500 to 30 µM with increasing incubation time from 1 to 24 h. The cytotoxic effects of H2O2 were also evaluated in neuroblastoma × spinal cord motor neuron cell line (NSC34). A short (30 min) exposure of H₂O₂ caused delayed cell death with the median effective concentration (EC₅₀) of ~1 mM ^[45]. Also, treatment of 500 μ M H₂O₂ for 24 h in a hippocampal neuronal cell line (HT-22) induces around 50% of cell death [46]. Further, investigation of exposure to 1 mM H₂O₂ for 2 h on human embryonic kidney 293 cells (HEK293) in vitro, cells displayed the extent of programmed cell death, with Condensed chromatin and apoptotic nuclei [47]. The above-reported studies and various other studies [48][49][50][51][52] elucidated H₂O₂ concentration-dependent change in cell signaling and death. Very low concentration of H₂O₂ cause cell signaling and hence, cell growth, a mid-higher concentration of around (120 μM to 150 μM) induce a temporary growth arrest, the intermediate concentration of (250 μM–400 μM) causes permanent growth arrest and a higher concentration of (≥ 1 mM) causes cell damage by necrosis and hence death.

3. Metabolic Sources and Sinks of Hydrogen Peroxide

The superoxide anion radical is the precursor of all radicals, and it is generated during the respiratory electron transport chain process complexed with cytochrome I, II, and III or by NAD(P)H oxidases (NOXs) enzymes in the mitochondria ^[53]. A total of 31 H_2O_2 generating oxidases have been reported ^[54]. Superoxide dismutases (SODs) like SOD1, SOD2, SOD3, with their presence in cytosolic, mitochondrial matrix, and extracellular locations,

respectively are the major sources of H_2O_2 . Besides that, the endoplasmic reticulum and peroxisomes are also responsible for the production of H_2O_2 ^[2]. There exist an H_2O_2 gradient, which is largely associated with their generation in association with respiratory cytochromes like complex III and is associated with the generation of H_2O_2 within mitochondrial cristae, whereas, complex I and II contribute H_2O_2 within the mitochondrial matrix ^[55]. The H_2O_2 removal from cells is mainly carried out by natural antioxidant enzymes like dismutation of catalases, peroxidases like glutathione peroxidases (GPxs), and peroxiredoxins in the form of H_2O and O_2 ^{[2][56][57]}. GPxs are a family of selenoenzymes homologous to selenocysteine, containing mammalian GPx-1, and have a high degree of affinity for H_2O_2 in humans. GPx-1 is one of the most expressed and abundant members of the GPx family of enzymes that include an epithelial-specific enzyme that is highly expressed in the intestine (GPx-2); a secreted subtype (GPx-3); and GPx-4, which is widely expressed and differs in its substrate specificity compared to the other family members. Accordingly, GPx-1 is a key selenoenzyme, an enzyme involved in alleviating the detrimental effects of H_2O_2 ^{[58][59]}. It is present in all cells; found in cytosolic, mitochondrial, and, in some cells, in peroxisomal compartments, GPx-1 can also reduce lipid hydroperoxides and other soluble hydroperoxides. GPx-4 ^[60] and GPx-7 ^[61] are also known to scavenge H_2O_2 in humans but are not globally expressed compared to GPx-1 ^[58].

4. Generation of Highly Unstable and Reactive Free Radical Species, the HO[•] from H₂O₂

Iron (Fe) is a component of various metalloproteins in living systems and is involved in several critical biochemical processes like oxygen transport through hemoglobin, electron transport during respiration in mitochondria, synthesis, and repair of nucleic acids, metabolism of xenobiotics, essential for oxidation-reduction catalysis and bioenergetics though heme of cytochrome enzymes [62]. Three major classes of Fe-containing proteins facilitate oxygen-based chemistry in living cells: iron-sulfur cluster-containing proteins; heme-containing proteins; and ironcontaining enzymes that are devoid of iron-sulfur clusters or heme. The redox ability of Fe makes it an indispensable metal of life, making it a key element in numerous biochemical processes of life [63]. However, the ability to take part in (oxidation, reduction cycle) renders Fe to act as a catalyst in a free state to generate toxic free radicals in oxygen-consuming organisms. For this reason, the circulating Fe is protected in a tightly bound state in form of Fe carrier transferrin, which keeps Fe in its inactive redox state. On the other hand, physiological cells also have some free Fe called labile Fe, which acts to generate free radical H_2O_2 , for redox signaling. However, any alteration in the normal pool of either bound or labile Fe in a state of redox disbalance will give stimulus to start Fenton chemistry to form one of the most toxic radical HO*. Over the last few decades, the role of Fe in neurodegenerative diseases has grabbed everybody's attention [64][65]. The requirement of Fe in the brain is high because of the high demand for energy [66][67]. Fe is an important component for the synthesis of neurotransmitters and myelin sheath of the neuron ^[68]. Fe toxicity due to Fe deposition and Fe-related oxidative damage is implicated in various neuropathology such as AD, PD, and ALS ^[69]. A large number of evidence suggests that Fe is involved in the onset and progression of ALS. Fe load was evident in the spinal cord of ALS patients [70], the motor cortex of ALS patients ^[71], gray matter from the frontal cortex of ALS patients ^[72], in the serum of ALS patients ^[73], and the

CSF of ALS patients ^[74]. Recent evidence has shown that oxidative burst due to Fenton chemistry is implicated in the pathology of ALS ^{[65][75][76][77]}.

Fe and H_2O_2 are involved in creating oxidizing environments inside living systems, causing the oxidation of biomolecules and hence cell damage. Being a transition metal, it has the capability to undergo oxidation and reduction inside living systems. Fe can react catalytically with H_2O_2 to form highly reactive and toxic species. Higher concentrations of H_2O_2 in the range of >100 nM cause disruptive redox signaling, causing oxidative distress and therefore, the oxidation of biomolecules. A higher concentration of H_2O_2 undergoes Fenton's reaction, which is a kind of disproportionation redox chemical reaction in the presence of ferrous ion (Fe⁺²) or Copper (Cu). The toxicity of H_2O_2 is mainly due to the generation of an OH[•] via the Fenton reaction in the presence of transition metal ion Fe or Cu, or via Haber–Weiss reaction in the presence of $O_2^{\bullet-178}$.

The OH^{*} is the most powerful oxidant among the reactive oxygen species (ROS), with a potential of $E^{0}(HO^{*}/H_{2}O) =$ 2.34 V. At very low pH, HO^{*} converts into its conjugate base O^{*-} (pKa(HO^{*};O^{*-}) = 11.9), the oxide radical, which is less reactive but not relevant at physiological pH ^[79]. The HO^{*} radical is electrophilic in nature and has a strong affinity towards aromatic and sulfur-containing biomolecules. There are three modes of action for the HO^{*} radical: electron abstraction, hydrogen abstraction, and double bond addition. The addition of HO^{*} radical causes oxidation of biomolecules, like 8-oxoguanine from guanine ^[80] and 2-oxo-histidine from histidine ^[81]. Whereas oxidation of sulfur-containing amino acid methionine (Met) forms Met sulphoxide and sulphone ^[82]. Electron abstraction is also observed with inorganic substrates like (Fe⁺²) ^[83]. The hydride anion (H⁻) abstraction mechanism is involved in reactions with various biomolecules, such as polyunsaturated fatty acids like linoleate and arachidonate ^[84], also from (SH) or hydroxyl (OH) functional groups from different proteins and peptides ^[85]. This HO^{*} initiates lipid peroxidation to form lipid peroxides ultimately leading to the formation of malonaldehyde or 4-Hydroxy-2-Nonenal (4-HNE), causing alteration in gene expression and promoting cell death ^[86].

 H_2O_2 can also be converted into a HO[•] in the presence of a superoxide radical anion ion called Heber-Weiss reaction ^{[79][87]}. Intriguingly, ascorbic acid, which is one of the antioxidants present in the lining of lungs and prevents the harmful effects of pollution, can also generate cytotoxic OH[•] when it is oxidized in the presence of hydrogen peroxide and transition metal catalyst like Fe and Cu in vitro ^[18]. This led to the development of acellular assays to measure particle-bound ROS and aerosol oxidative potential (OP) of the particulate matter present in air pollution ^[88]. Furthermore, it is important to note that, ascorbic acid acts as a pro-oxidant and recycles the ferric ion (Fe⁺³) to (Fe⁺²), hence, facilitating and enhancing the generation of ROS, through successive Fenton cycles ^[89].

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