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Hydroxyl radical is a significant player in oxidative DNA damage *in vivo*

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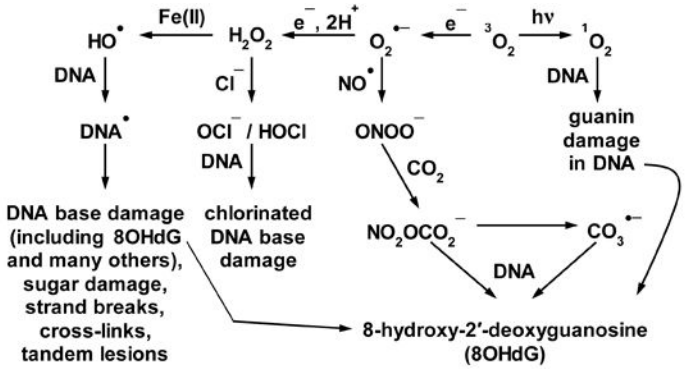
Graphical Abstract



Schematic representation of the important chemical reactions involved in reactive oxygen species-mediated DNA damage

Short Statement

Recent publications have suggested that oxidative DNA damage mediated by hydroxyl radical (•OH) is unimportant *in vivo*, and that carbonate anion radical ($CO_3^{\bullet-}$) plays the key role. We examine these claims and summarize the evidence that •OH does play a key role as an important member of the reactive oxygen species (ROS) *in vivo*.

1. Introduction to reactive oxygen species and DNA damage

A wide range of reactive oxygen species (ROS) is formed *in vivo* in the human body and in other living organisms (reviewed in [1]). The term “reactive” covers a broad spectrum: some ROS, such as superoxide anion radical ($O_2^{\bullet-}$), nitric oxide (NO•) and hydrogen peroxide

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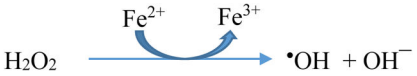
(H_2O_2) are very selective in their reactions. Others, such as hypochlorous acid (HOCl), carbonate anion radical ($CO_3^{\bullet-}$) and the two singlet states of oxygen ($^1O_2$), are fiercer and can attack several biomolecules. By contrast, the hydroxyl radical ($^{\bullet}OH$) reacts at or near a diffusion-controlled rate with almost every organic biomolecule found in living organisms [1, 2]. Several ROS, generally the ones of lower reactivity such as H_2O_2 and $NO^{\bullet}$, play important physiological roles *in vivo*, but the ones of higher reactivity can cause oxidative damage to biomolecules, resulting in impairment of cellular functions (reviewed in [1, 3]). In particular, oxidative damage to DNA plays an important role in the origin and progression of a number of human diseases, most prominently cancer but also others, such as neurodegenerative diseases and atherosclerosis [1, 4–6]. The ability of several ROS to attack DNA and generate mutagenic end-products plays a key role in cancer development in humans. Much attention has been paid to the mutagenic lesion 8-hydroxy-2′-deoxyguanosine (8OHdG) in this context [1, 7], but many other mutagenic and/or cytotoxic lesions are formed when $^{\bullet}OH$ attacks DNA [1, 5, 8–15]. However, recent articles [16–18] have suggested that $^{\bullet}OH$ is not involved in DNA damage caused by oxidative stress and argue a key role instead for $CO_3^{\bullet-}$, which attacks guanine residues in DNA to form 8OHdG. We would like to bring two matters to the attention of the journal readership,

1. that there is much more to biologically-significant oxidative DNA damage than only 8OHdG formation, and
2. that $^{\bullet}OH$ does play a significant role in causing oxidative DNA damage *in vivo*.

2. How does hydroxyl radical arise in *vivo*?

Hydroxyl radical is generated *in vivo* by several mechanisms, including:

a. through the reaction of certain transition metal ions (especially Fe^{2+} and Cu^{+} (reaction 1, Fenton reaction) with H_2O_2 (reviewed in [1, 3]).



(1)

The question of the availability, catalytic activity and chemical nature of transition metal ions *in vivo* has been repeatedly discussed [1, 3, 19–21], but there is no clear consensus as yet, although the recent discovery of ferroptosis, a form of iron ion-induced cell death, has rekindled interest in this topic [3, 22]. For example, Fe^{2+} ions bound to phosphate, polyphosphate, citrate, ATP etc. have shown variable activities in $^{\bullet}OH$ generation *in vitro* [1, 21–28], but these simple studies in solution rarely reflect the complex cellular and extracellular environment *in vivo* (which is enormously rich in proteins, lipids, nucleic acids and hundreds of different metabolites). We return to this question in Section 4 below.

b. in certain circumstances, by homolysis of H_2O_2 (reaction 2, reviewed in [1]).

$$H_2O_2 \rightarrow 2 \bullet OH \quad (2)$$

c. The fission of H_2O upon exposure to ionizing radiation (to which we have a constant background exposure [1, 9, 31]). Water cation radical ($H_2O^{\bullet +}$) is the primary species formed in the physical stage (~10^{-15}s) due to the interaction of ionizing radiation with water (reviewed in [31]). Subsequently, there is ultrafast proton transfer from $H_2O^{\bullet +}$ in the physicochemical stage (10^{-15} – 10^{-12} s) to a surrounding water molecule (reaction 3).

$$H_2O^{\bullet +} + H_2O \rightarrow \bullet OH + H_3O^{\bullet +} \quad (3)$$

In addition, $^{\bullet}$OH is formed by homolysis (reaction 4) of the excited water molecule ($(H_2O)^*$) [1, 9, 31].

$$(H_2O)^* \rightarrow \bullet OH + H^{\bullet} \quad (4)$$

Indeed, the damage that $^{\bullet}$OH causes to DNA helps to explain why exposure to ionizing radiation can lead to cancer development [1, 4, 5, 9].

That $^{\bullet}$OH is generated *in vivo* (including by Fenton chemistry) has been demonstrated by a multiplicity of methods, including aromatic hydroxylation and ESR spin trapping [1, 32–42]. Owing to its high electrophilicity and high reactivity [1, 2, 9], $^{\bullet}$OH reacts at or near a diffusion-controlled rate (rate constant >10^9 $M^{-1}s^{-1}$) with almost all organic biomolecules. As a result, when $^{\bullet}$OH is generated *in vivo*, it will attack whichever of these organic molecules are adjacent to it [1, 2, 9].

3. The role of bicarbonate *in vivo*

As mentioned, recent articles [16–18] have argued that $CO_3^{\bullet -}$ and not $^{\bullet}$OH plays the major role in causing oxidative DNA damage *in vivo.* It is well known that bicarbonate anion (HCO_3^-) is important in maintaining physiological pH and is indeed present intracellularly at high mM (10–40 mM) concentration [16–18 and references therein]. *In vitro* studies have suggested that in the presence of HCO_3^- the reaction of Fe^{2+} and H_2O_2 does not generate $^{\bullet}$OH but instead $CO_3^{\bullet -}$ [16–18, 43]. An alternative explanation is that $^{\bullet}$OH is generated but immediately reacts with HCO_3^- to give $CO_3^{\bullet -}$. However, the rate constant for the formation of $CO_3^{\bullet -}$ via H-atom abstraction from HCO_3^- by $^{\bullet}$OH (reaction 5) under physiological conditions has been measured by pulse radiolysis and is found to be quite low, 8.5×10^6 $M^{-1}s^{-1}$ [44].

$$HCO_3^- + \bullet OH \rightarrow CO_3^{\bullet -} + H_2O \quad (5)$$

Molecules such as 2′-deoxyribose phosphate, the purine and pyrimidine bases of DNA and RNA, reduced glutathione (GSH) and proteins, present *in vivo* also at substantial concentrations, react much faster with $^{\bullet}$OH, at diffusion-controlled rates (>10^9 $M^{-1}s^{-1}$) and

so may be preferred targets, depending on the location and environment in which the $^{\bullet}OH$ is generated [1, 2, 6, 8, 9], as we discuss in Section 4. However, $CO_3^{\bullet-}$ (and possibly some $^{\bullet}OH$) can also be generated in pathways involving $NO^{\bullet}$, CO_2 and peroxynitrite (reviewed in [1, 45, 46]). The rate constant of the reaction of CO_2 with peroxynitrite involved in this process, ranges from 3×10^4 M^{-1} s^{-1} to 5.8×10^4 M^{-1} s^{-1} [1, 45, 46].

4. The relative reactivities of $^{\bullet}OH$ and $CO_3^{\bullet-}$ with DNA

Two approaches can throw light on this question, an examination of thermodynamic parameters and direct experimental studies. The absolute reduction potentials (E°) and midpoint potentials (E_7) of $^{\bullet}OH$, $CO_3^{\bullet-}$, and the DNA components are presented in Table 1 below [8, 47–50].

From Table 1 and assuming the E_7 of $^{\bullet}CH_2CH_3$ [48] and of dR [49] as a guide for that of the sugar moiety in DNA, we conclude that $CO_3^{\bullet-}$ is very unlikely to cause oxidative damage to dR and pyrimidines and should be capable of oxidizing only guanine , and perhaps adenine to a much lesser extent. Following the ionization potentials of the bases and according to Table 1 above, guanine should be the major or only site of oxidative damage by $CO_3^{\bullet-}$ in DNA. Indeed, a combination of laser flash photolysis and product analysis studies has confirmed that $CO_3^{\bullet-}$ oxidizes guanine in DNA, to form 8OHdG [45, 51]. We can find no literature evidence of adenine oxidation by $CO_3^{\bullet-}$. Also, if $CO_3^{\bullet-}$ were the main player in oxidative DNA damage, as argued in [16–18] and due to the repulsive forces of the highly negative charged polymer (DNA) and $CO_3^{\bullet-}$, we should not expect $CO_3^{\bullet-}$ mediated sugar-phosphate damage leading to strand break formation and indeed this is scarcely observed [51, 52].

In agreement with the E° values in Table 1, direct experimental results show that when $^{\bullet}OH$ reacts with DNA it forms a multiplicity of damage products (Figure 1) from all four purine and pyrimidine bases and from the dR moiety [1, 8–14, 53, 54]. No other known ROS forms such a wide range of products: some (such as H_2O_2 and $O_2^{\bullet-}$) do not react directly with DNA at all whereas others (e.g. $CO_3^{\bullet-}$, $^1O_2$) target guanine selectively [1, 8, 16]. Hence, the demonstration that this wide range of products (shown in Figure 1) is formed *in vivo* is excellent evidence that $^{\bullet}OH$ has been generated and has attacked DNA, whatever studies on simplified systems *in vitro* that do not reflect the complex cellular environment *in vivo* may suggest. To take one example, when human respiratory tract epithelial cells were exposed to 100 μM H_2O_2, there was rapid induction of DNA strand breakage and chemical modifications to all 4 DNA bases, diagnostic of attack by $^{\bullet}OH$ [53]. How can this diagnostic damage pattern of $^{\bullet}OH$ attack be explained, since H_2O_2 does not react with DNA? We have already mentioned our poor knowledge of the availability and distribution of transition metal ions *in vivo*, but evidence suggests that DNA *in vivo* has transition metal ions such as Fe^{2+} and Cu^{+} bound to it, given its very strong negative charge due to the phosphate groups (reviewed in [1]). Indeed, Fe^{2+} bound to phosphate is generally agreed (even by Prof. Burrows [17]) to generate $^{\bullet}OH$ from H_2O_2, and the reasons for this have been recently elucidated [55]. The phosphate levels in the nucleus are very high due to the phosphate residues in DNA and so $^{\bullet}OH$ formation will be favoured. H_2O_2 crosses plasma and intracellular membranes reasonably freely [1] and, if it reaches the nucleus, H_2O_2 can react

with such metal ions to generate •OH directly upon the DNA, causing immediate oxidative damage, often called “site-specific” damage [1, 2]. This “site-specific” damage by localized •OH generation also occurs with biomolecules other than DNA, such as proteins, again generating multiple products diagnostic of •OH attack [1, 56, 57]. It cannot be prevented by external molecules that scavenge •OH, such as HCO_3^-, glucose or GSH [1]. Furthermore, the formation of a thymine-tyrosine crosslink has been observed upon treatment of mammalian cells with Fe(II), and involvement of •OH has been suggested in this crosslink formation [58]. The free radical mechanistic pathways of •OH - mediated formation of multiple guanine and other DNA base damage products that are produced via oxidative damage, have been well documented in the literature [1, 6, 8, 12, 59].

The exact molecular ratios of different DNA base and sugar damage products generated by site-specific •OH formation or other modes of •OH attack upon DNA depend on several factors, including where upon the DNA the metal ions are bound [9–12]. This pattern of multiple DNA base damage products is indeed observed *in vivo*: low levels of multiple base DNA damage products are present in DNA from all human and other animal tissues examined and the levels increase when oxidative stress is imposed by a variety of mechanisms [1, 6, 8–14, 59–64], e.g. in diabetes [65]. For example, 8,5′-cyclopurine-2′-deoxynucleosides in DNA are generated exclusively by •OH attack upon 2′-deoxyribose units generating C5′ radicals, followed by cyclization with the C8 position of the purine base [59, 66, 67]. This vast literature unequivocally demonstrates the formation of •OH-induced DNA base and 2′-deoxyribose products *in vivo*. In addition, oxidative stress can liberate catalytically-active transition metal ions (especially iron ions) from a range of cellular proteins (such as iron-sulphur proteins, and ferritin) [1, 19, 29, 68, 69], and some of these may bind to DNA, making it a further *in vivo* target of oxidative damage by site-specific •OH generation [1].

5. There is much more to biologically-significant oxidative DNA damage than 8OHdG formation

Apart from 8OHdG, the importance of many other DNA lesions, some of which are shown in Fig. 1, in cancer development *in vivo* has been highlighted, and the existence of DNA repair enzymes needed for their removal and whose genetic deletions increase cancer development in animals is further evidence that these mutagenic and/or cytotoxic lesions are formed in *vivo* and are important in the development of cancer and other diseases [1, 8, 70, 71].

6. Conclusion

There is unequivocal evidence of the •OH-specific pattern of oxidative DNA damage *in vivo* and in isolated cells subjected to oxidative stress. This, combined with the ability to trap •OH by specific methods in living systems, provides substantial evidence that •OH plays an important role in oxidative DNA damage, and other aspects of oxidative damage, including protein and lipid damage, *in vivo* [1]. This is in part due to formation of 8OHdG, which can also be generated by attack of $^1O_2$ and of $CO_3^{\bullet-}$ on DNA, but also due to many other mutagenic and/or cytotoxic lesions, formed from purines, pyrimidines and 2′-deoxyribose

by •OH attack (Fig. 1). Carbonate anion radical might also play an important role *in vivo* [16–18]. Certain other ROS, such as HOCl, can also attack DNA. Hypochlorous acid forms chlorinated base products, which have indeed been detected *in vivo* [72, 73].

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements

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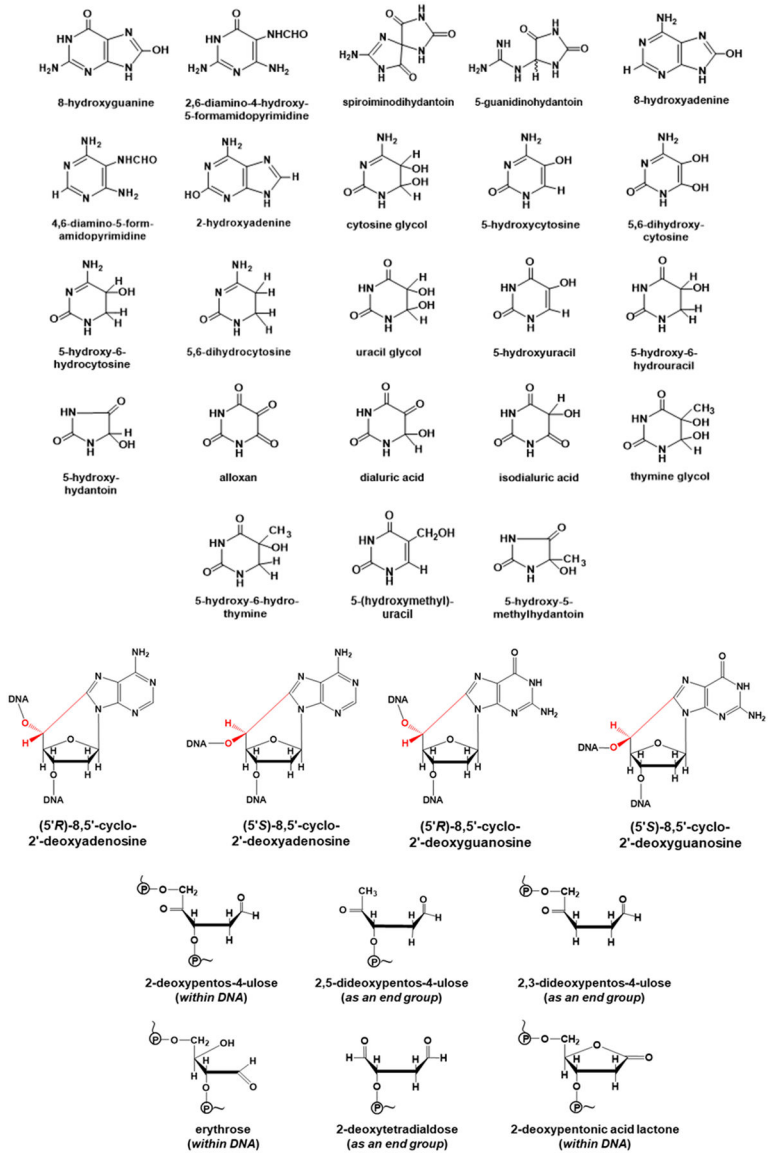

Figure 1. Products resulting from attack of hydroxyl radicals on DNA

By contrast, carbonate anion radical modifies only guanine residues

Table 1.

The absolute reduction potentials (E°) and the midpoint potential (E_7) of $^{\bullet}OH$, $CO_3^{\bullet-}$ and of base cation radicals. The E_7 value of 2′-deoxyribose (dR) is also listed.

Bases and radical	E vs. SHE (V)			
	Couple (E°)	E° in DMF	Couple (E_7)	E_7 by pulse radiolysis in water
G (Guanine base)	($G^{\bullet+}$/G)	1.49	(G(N1–H)$^{\bullet}$)/H^+, G)	1.29
A (Adenine base)	($A^{\bullet+}$/A)	1.96	(A(N6–H)$^{\bullet}$)/H^+, A)	1.42
C (Cytosine base)	($C^{\bullet+}$/C)	2.14	(C(N4–H)$^{\bullet}$)/H^+, C)	1.6
T (Thymine base)	($T^{\bullet+}$/T)	2.11	(T(N3–H)$^{\bullet}$)/H^+, T)	1.7
$^{\bullet}OH$			$^{\bullet}OH$, H^+/H_2O	2.3
$CO_3^{\bullet-}$			$CO_3^{\bullet-}/CO_3^{2-}$	1.59
$^{\bullet}CH_2CH_3$			$^{\bullet}CH_2CH_3$, H^+/CH_3CH_3	1.9
dR$^{\bullet}$			dR$^{\bullet}$ / H^+, dR	>1.8