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Cr(III)-mediated hydroxyl radical generation via Haber-Weiss cycle

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Abstract

ESR spin trapping and HPLC were utilized to investigate Cr(III)-mediated hydroxyl radical ($^{\bullet}OH$) generation via the following Haber-Weiss reactions in vitro:

$$Cr(III) + O_2^{\bullet -} \rightarrow Cr(II) + O_2$$

$$Cr(II) + H_2O_2 \rightarrow Cr(III) + {}^{\bullet}OH + OH^-$$

Xanthine and xanthine oxidase were used as a source of superoxide ($O_2^{\bullet -}$) and H_2O_2. A mixture of xanthine and xanthine oxidase in the presence of the spin trapping agent, 5,5-dimethyl-pyrroline N-oxide (DMPO), generated DMPO/$O_2^{\bullet -}$. Addition of Cr(III) to this mixture generated DMPO/$^{\bullet}$OH. Catalase partially inhibited DMPO/$^{\bullet}$OH formation, while the combination of catalase and superoxide dismutase (SOD) completely blocked the generation of DMPO/$^{\bullet}$OH. The reaction of Cr(III) with H_2O_2, itself, also generated DMPO/$^{\bullet}$OH. This H_2O_2 enhanced DMPO/$^{\bullet}$OH formation was significantly increased in the presence of xanthine, and xanthine oxidase. Metal chelators, deferoxamine, 1,10-deferoxamine and EDTA, decreased Cr(III)-dependent $^{\bullet}$OH generation. Parallel ESR spin trapping measurements were carried out using Cr(VI). Although Cr(III) generated $^{\bullet}$OH via a Haber-Weiss cycle, the relative yield of the $^{\bullet}$OH formation was comparable to that of a Fe(II)-mediated one but lower than that generated by a Cr(VI)-mediated Haber-Weiss cycle. HPLC measurements also show that the $^{\bullet}$OH radical generated via a Cr(III)-mediated Haber-Weiss reaction was capable of causing 2′-deoxyguanosine (dG) hydroxylation to generate 8-hydroxyl-2′-deoxyguanosine (8-OHdG). The relative yield of 8-OHdG formation correlated with the generation of $^{\bullet}$OH as measured by ESR spin trapping. The results suggest that Cr(III)-mediated $^{\bullet}$OH radical generation may contribute to the mechanism of Cr(III)- and Cr(VI)-induced carcinogenesis.

1. Introduction

Cr(VI)-containing compounds are major environmental contaminants with human exposure occurring through air, food and water [1] and are well established carcinogens [2]. Epidemiological studies have shown that workers exposed to Cr(VI) had a higher incidence of respiratory cancers than the general population [3]. In experimental animals, Cr(VI) compounds also induce tumors [4–6]. Studies have reported the occurrence of tumors at the injection and implantation sites. For example, intrabronchial implantation of chromate compounds in rats resulted in bronchial carcinomas, whereas intramuscular implantations and intrapleural and subcutaneous injections in rats and mice resulted in injection site sarcomas. Cr(III), on the other hand, is believed to be relatively inocuous and is considered to be noncarcinogenic in humans. The different biological effects of Cr(VI) and Cr(III) are believed to be due to the cellular uptake process [7]. Cr(VI) actively enters the cells via the surface anion transport system and is biologically active [7]. Although Cr(III) binds to DNA in cell free system, it is poorly taken up by the cells [7], and Cr(III) compounds have not been shown to be

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carcinogenic or mutagenic in animal or epidemiological studies [8]. Since Cr(VI) is unreactive with DNA in cell-free systems, reduction of Cr(VI) by cellular reductants to lower oxidation states has been considered an important step in the mechanism of Cr(VI)-induced DNA damage [7]. We have shown that Cr(VI) can be reduced by various cellular reductants, including ascorbate [9], glutathione reductase [10] and microsomes/NAD(P)H [11], to generate Cr(V), which reacts with H_2O_2 to generate $^{\bullet}OH$ radical via a Fenton-like reaction [9–12]. This result led to intensive investigation on the role of Cr(V)-mediated free radical generation in the mechanism of Cr(VI)-induced carcinogenesis [13–17].

While recent studies have demonstrated that Cr(V) and related free radical generation play important roles in the mechanism of Cr(VI)-induced carcinogenesis [13–17], there are relatively few studies concerning the role of Cr(III) [18,19]. Cr(VI) may be more carcinogenic than Cr(III) because Cr(VI) can actively enter the cells [7]. Inside the cells, Cr(VI) is readily reduced to lower oxidation states, Cr(V) and Cr(IV), and eventually to Cr(III) [7]. Although once within cells Cr(III) has been reported to be carcinogenic, the underlying mechanism is not very clear. In our recent study [18], hydroxy radical ($^{\bullet}OH$) generation by Cr(III) from H_2O_2 has been demonstrated. It has been suggested that the Cr(III)/Cr(II) redox couple serves as cyclical electron donors in a Fenton-like reaction to generate reactive oxygen species [19]. Certain biological reductants, penicillamine, cysteine and glutathione, have been shown to reduce Cr(III) to Cr(II) [20]. NADH and cysteine have also been shown to reduce Cr(III) to Cr(II) [21]. In the present study, $O_2^{\bullet-}$ was chosen as a possible Cr(III) reductant. The following questions will be examined. (a) Does Cr(III) generate $^{\bullet}OH$ via Haber-Weiss reactions (Eqs. (1)–(3))?

$$Cr(III) + O_2^{\bullet-} \rightarrow Cr(II) + O_2 \quad (1)$$

$$Cr(II) + H_2O_2 \rightarrow Cr(III) + {}^{\bullet}OH + OH^- \quad (2)$$

Overall

$$H_2O_2 + O_2^{\bullet-} \xrightarrow{Cr(III)/Cr(II)} O_2 + {}^{\bullet}OH + OH^- \quad (3)$$

(b) If $^{\bullet}OH$ radicals are indeed generated by the above reactions, how does it compare with that generated by Cr(VI)-mediated Haber-Weiss reactions? (c) Are $^{\bullet}OH$ radicals, generated in these reactions (Eqs. (1)–(3)), capable of causing 2′-deoxyguanosine (dG) hydroxylation to generate 8-hydroxyl-2′-deoxyguanosine (8-OHdG)?

2. Materials and methods

Chromium acetate (Cr(III)), 2′-deoxyguanosine (dG), deferoxamine, ethylenediaminetetraacetic acid (EDTA), diethylenetriaminepentaacetic acid (DTPA), 1,10-phenanthroline, H_2O_2, xanthine, and xanthine oxidase (bovine milk) were purchased from Sigma (St. Louis, MO). Catalase from beef liver (65,000 U/ml) and superoxide dismutase (SOD) from bovine erythrocytes (containing Cu/Zn, 5000 U/mg) were purchased from Boehringer–Mannheim (Indianapolis, IN). 5,5-Dimethyl-pyrroline N-oxide (DMPO) was purchased from Aldrich (Milwaukee, WI) and was purified by charcoal decolorization and vacuum distillation. The DMPO solution thus purified did not contain any ESR-detectable impurities. Chelex-100 chelating resin was purchased from Bio-rad Laboratories (Richmond, CA). The phosphate buffer (pH 7.4) was treated with Chelex-100 to remove transition metal ion contaminants.

ESR spin trapping was used for detecting short-lived free radical intermediates. All ESR measurements were made using a Varian E4 spectrometer and a flat cell assembly. Hyperfine splittings were measured (to 0.1 G) directly from magnetic field separation using 1,1-diphenyl-2-picryl-hydrazyl (DPPH) as a reference standard for g value. The relative radical concentration was estimated by multiplying half of the peak height by $(\Delta H_{pp})^2$ (where ΔH_{pp} represents peak-to-peak width). Reactants were mixed in test tubes and then transferred to a flat cell for ESR measurement. The concentrations given in the figure legends are final concentrations. All experiments were carried out at room temperature.

A BAS 200A HPLC system was used for HPLC measurements using a biophase ODS C_{18} column (4.6×250 mm). The solvent used for elution was a mixture of 50 mM KH_2PO_4/7% methanol at a flow rate of 1.5 ml/min. The 8-OHdG was monitored at 254 nm UV detector and by an electrochemical detector set at 700 mV and 5–50 nA full scale. Under these conditions, the retention time for dG was 9.7 min and that for 8-OHdG was 13.7 min. The identification of the 8-OHdG peaks in experimental samples was determined by spiking the sample with a known sample of synthetic 8-OHdG. The HPLC system was calibrated with a standard solution of dG and 8-OHdG.

3. Results

Xanthine and xanthine oxidase are known to be able to reduce molecular oxygen and generate $O_2^{\bullet-}$ and H_2O_2 and are used in this study as a source of $O_2^{\bullet-}$ and H_2O_2. Fig. 1(a) shows the ESR signal obtained 40 s after reaction initiation from a mixture of 0.1 units/ml xanthine oxidase, 0.5 mM xanthine and 200 mM DMPO in phosphate buffer (pH 7.4). Analysis of this spectrum shows hyperfine splittings of $a_N = 14.2$ G, $a_H = 11.5$ G and $a_H^{\gamma} = 1.2$ G. These splittings are typical of DMPO/$O_2^{\bullet-}$ [22]. When the spectrum was recorded 3 min after reaction initiation, the 1:2:2:1 quartet with hyperfine splittings of $a_N = a_H = 15.0$ G was obtained, which was the decay product of DMPO/$O_2^{\bullet-}$ and was assigned as DMPO/$^{\bullet}OH$ (Fig. 1(b). When Cr(III) was added to the reaction mixture, a significantly stronger DMPO/$^{\bullet}OH$ signal was obtained (Fig. 2(a)). For verification of $^{\bullet}OH$ detection, we carried out competition experiments in which the $^{\bullet}OH$ radical abstracts a hydrogen atom from ethanol to generate the ethanoyl ($^{\bullet}CHOHCH_3$) radical. The $^{\bullet}CHOHCH_3$ is trapped

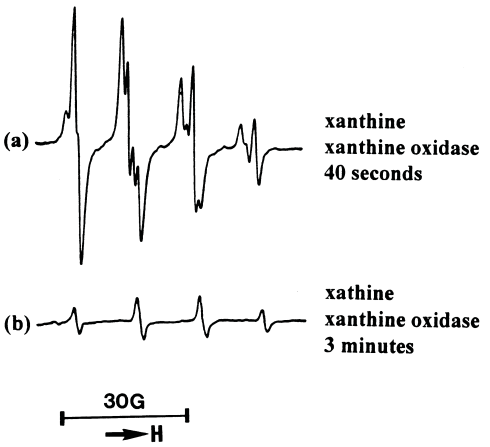

Fig. 1. (a) ESR spectrum, recorded 40 s after reaction initiation, from a pH 7.4 phosphate buffer solution containing 200 mM DMPO, 0.5 mM xanthine, 0.1 U/ml xanthine oxidase; (b) same as (a) but the spectrum was recorded 3 min after reaction initiation. The ESR spectrometer settings were: receiver gain, 2.5×10^3; modulation amplitude, 0.4 G; scan time, 2 min; magnetic field, 3470 ± 100 G.

by DMPO as DMPO/$^{\bullet}CHOHCH_3$ adduct which exhibits different hyperfine splittings from DMPO/$^{\bullet}OH$. As expected, addition of ethanol resulted in appearance of a spin adduct signal with the splitting constants $a_N = 15.8$ G and $a_H = 22.8$ G (data not shown). These splitting constants are characteristic for the DMPO/$^{\bullet}CHOHCH_3$ adduct, showing that $^{\bullet}OH$ radicals are generated in the mixture. Addition of catalase partially decreased the intensity of DMPO/$^{\bullet}OH$ (Fig. 2(b)), while addition of both catalase and SOD completely eliminated the generation of DMPO/$^{\bullet}OH$ (Fig. 2(c)). When H_2O_2 was added to a mixture of xanthine, xanthine oxidase and Cr(III), a much stronger DMPO/$^{\bullet}OH$ signal was observed (Fig. 2(d)). A mixture of Cr(III) and H_2O_2 alone generated DMPO/$^{\bullet}OH$ (Fig. 2(e)) as reported earlier [18]. ESR measurements were also made from a mixture containing Fe(II), xanthine and xanthine oxidase. The spectrum is shown in Fig. 2(f)). As can be noted from these data, Cr(III) generated a stronger DMPO/$^{\bullet}OH$ signal from xanthine and xanthine oxidase than that of Fe(II), a typical Fenton/Haber-Weiss reagent.

In an earlier study [23], we have shown that $O_2^{\bullet -}$ is able to reduce Cr(VI) to Cr(V). In this study we measured the Cr(V) generation and $^{\bullet}OH$ formation and compared it with that of Cr(III). Fig. 3(a) shows a typical ESR spectrum obtained from a mixture of xanthine, xanthine oxidase, NADH, and Cr(VI). The NADH was added for the detection of Cr(V) because reaction of this reactive chromium intermediate with NADH generates a relatively stable Cr(V)-NADH complex, which can be detected by ESR [6]. The 1:2:2:1 quartet was assigned to a DMPO/$^{\bullet}OH$ adduct. The peak at $g = 1.9792$ was assigned to Cr(V). Addition of SOD sharply decreased the generation of both $^{\bullet}OH$ radicals and Cr(V) (Fig. 3(b)). Addition of catalase also decreased the $^{\bullet}OH$ generation but drastically increased the Cr(V) formation (Fig. 3(c)). The intensity of Cr(V) peak was so strong that four satellite peaks (as indicated by asterisks in Fig. 3(c)) due to ^{53}Cr (9.55%, abundance, $I = \frac{3}{2}$) were observed. Addition of H_2O_2 caused about a 10-fold increase in $^{\bullet}OH$ generation while the Cr(V) signal was eliminated (Fig. 3(d)).

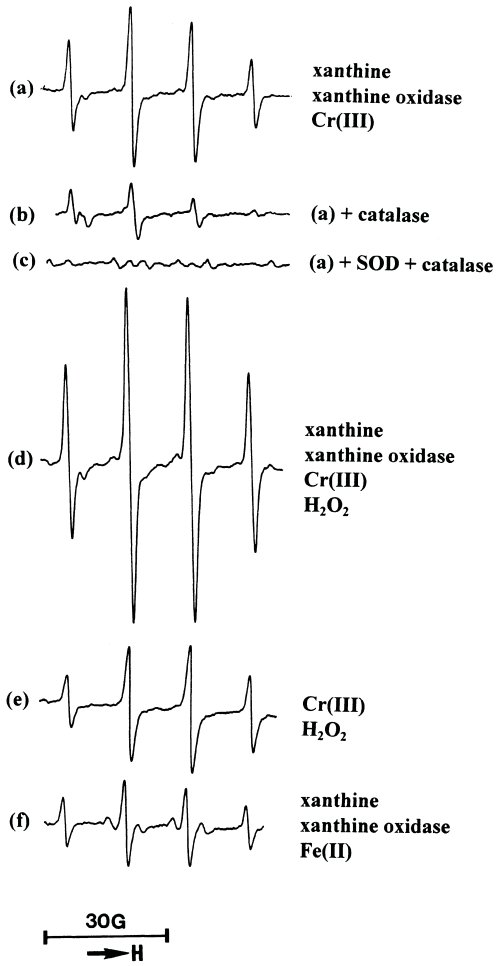

Fig. 2. (a) ESR spectrum, recorded 3 min after reaction initiation, from a pH 7.4 phosphate buffer solution containing 200 mM DMPO, 2 mM Cr(III), 0.5 mM xanthine, 0.1 U/ml xanthine oxidase; (b) same as (a) but with 2000 units/ml catalase added; (c) same as (a) but with 2000 units/ml catalase and 500 units/ml SOD added; (d) same as (a) but with 0.5 mM H_2O_2 added; (e) The reaction mixture containing 2 mM Cr(III) and 0.5 mM H_2O_2 with other conditions the same as (a); (f) The reaction mixture containing 0.5 mM xanthine, 0.1 U xanthine oxidase and 0.5 mM Fe(II) with other conditions the same as (a). The spectrometer settings were: receiver gain, 2.5×10^3; modulation amplitude, 0.4 G; scan time, 2 min; magnetic field, 3470 ± 100 G.

Table 1 shows the effect of chelators on $^{\bullet}OH$ generation in a mixture of Cr(III), xanthine and xanthine oxidase. The chelators tested, EDTA, 1,10-phenanthroline and deferoxamine, reduced the signal intensity of DMPO/$^{\bullet}OH$ by about 49%, 32% and 32%, respectively.

HPLC with electrochemical detection was used to examine dG hydroxylation caused by Cr(III) reaction. 8-OHdG eluted at 13.7 min and dG at 9.7 min. A representative chromatogram is shown in Fig. 4. A sample

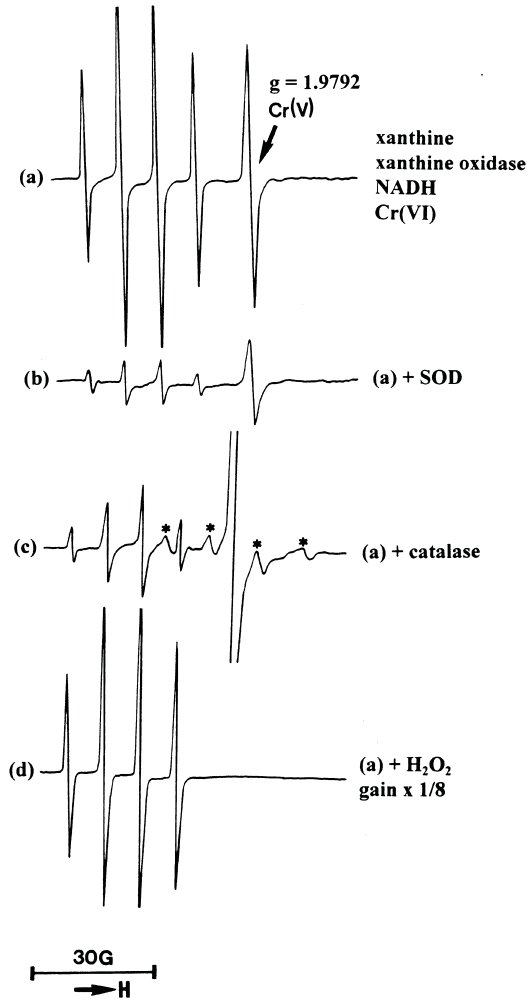

Fig. 3. (a) ESR spectrum, recorded 3 min after reaction initiation, from a pH 7.4 phosphate buffer solution containing 200 mM DMPO, 2 mM Cr(VI) as $K_2Cr_2O_7$, 0.5 mM xanthine, 0.1 U/ml xanthine oxidase; (b) same as (a) but with 500 units/ml SOD added; (c) same as (a) but with 2000 units/ml catalase added; (d) same as (a) but with 1.5 mM H_2O_2 added. The asterisks indicates four satellite signals due to ^{53}Cr (9.55% abundance, $I = \frac{3}{2}$). The spectrometer settings were: receiver gain, 1.0×10^3 (except 1.00×10^2 for (d)); modulation amplitude, 0.4 G; scan time, 2 min; magnetic field, 3470 ± 100 G.

Table 1
Effect of chelators on relative concentration of Cr(III)-generated DMPO/•OH

Relative DMPO/•OH	Chelator
1.00	No chelator
0.51	Deferoxamine
0.68	EDTA
0.68	1,10-Phenanthroline

The reaction mixture contained 200 mM DMPO, 2 mM Cr(III), 0.5 mM xanthine; 0.1 U/ml xanthine oxidase, 0.5 mM H_2O_2, and chelators as indicated, in phosphate buffer solution (pH. 7.4). The spectra were recorded 3 min after reaction initiation. The relative DMPO/•OH concentration was estimated by multiplying half of the peak height by $(\Delta H_{pp})^2$ (where ΔH_{pp} represents peak-to-peak width).

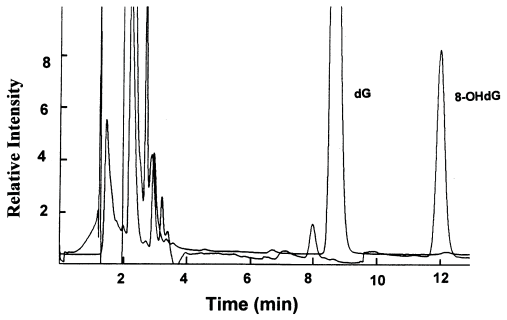

Fig. 4. HPLC fraction of dG with incubation of 2 mM Cr(III), 0.25 mM xanthine, 0.25 units/ml xanthine oxidase. The reaction mixture were incubated in a pH 7.4 phosphate buffer at room temperature for 24 h under ambient air.

containing synthetic 8-OHdG increased the peak intensity, but did not alter the elution time. 8-OHdG in the sample and synthetic 8-OHdG show essentially the same elution time, affirming the formation of 8-OHdG in the incubation mixture. Table 2 shows the comparison of 8-OHdG formation from various Cr(III) reactions. A mixture of dG, Cr(III), xanthine, and xanthine oxidase incubated for 24 h generated 23.5 ± 2.3 pmol 8-OHdG/μg dG. Omission of any one component sharply decreased the 8-OHdG generation. Addition of H_2O_2 to this mixture enhanced the generation of 8-OHdG. Formate, an •OH radical scavenger, decreased 8-OHdG generation. Metal ion chelators, deferoxamine, 1,10-phenanthroline and EDTA, also decreased the 8-OHdG generation. Replacement of Cr(III) with Cr(VI) caused a significant enhancement in the 8-OHdG yield.

4. Discussion

The results obtained from the present study demonstrate that Cr(III) is capable of generating •OH radicals through Haber-Weiss reactions. The Cr(III)-mediated Haber-Weiss mechanism of •OH generation could be particularly significant during phagocytosis (upon exposure to Cr-containing respirable particles). In this process, macrophage and other cellular constituents generate large quantities of $O_2^{\bullet -}$ radicals during the so-called "respiratory burst" [24]. During the respiratory burst, a substantial portion of the oxygen consumption by phagocytes is converted to $O_2^{\bullet -}$. Further conversion of $O_2^{\bullet -}$ to •OH is too slow to be biologically significant, unless a suitable metal ion is present as a Haber-Weiss catalyst. The present study shows that Cr(III) is such a Haber-Weiss catalyst. In addition, using NADH as a Cr(V) chelating (trapping) agent, this study shows that Cr(VI) is readily reduced to Cr(V). The Cr(V) intermediates react with H_2O_2 to generate •OH radical. The data indicate that the relative yield of Cr(III)-mediated •OH generation via Haber-Weiss reactions is lower than that generated by Cr(VI) through similar reactions. However, since it has been reported that Cr(III) is able to bind to DNA[25], Cr(III) may cause significant DNA

Table 2
Hydroxylation of dG by Cr(III) and Cr(VI) reactions

Reaction mixture	8-OHdG/dG (pmol/μg dG ± SD (n = 3))
dG + Cr(III) + xanthine + xanthine oxidase	23.5 ± 2.3
dG + Cr(III)	Nondetectable
dG + Cr(III) + xanthine + xanthine oxidase + H_2O_2	52.7 ± 4.1
dG + H_2O_2	2.3 ± 0.4
dG + Cr(III) + H_2O_2	14.3 ± 1.1
dG + Cr(III) + xanthine + xanthine oxidase + H_2O_2 + formate	3.5 ± 0.61
dG + Cr(III) + xanthine + xanthine oxidase + H_2O_2 + deferoxamine	24.9 ± 1.61
dG + Cr(III) + xanthine + xanthine oxidase + H_2O_2 + 1,10-phenanthroline	38.4 ± 2.19
dG + Cr(III) + xanthine + xanthine oxidase + H_2O_2 + EDTA	36.1 ± 2.19
dG + Cr(VI) + xanthine + xanthine oxidase + H_2O_2	184.5 ± 8.9

Concentrations of reactants were as follows: dG, 1 mM; Cr(III), 2 mM; Cr(VI), 2 mM; xanthine, 0.25 mM; xanthine oxidase 0.25 units/ml; H_2O_2; 1 mM; formate, 50 mM; deferoxamine, 2 mM; 1,10-phenanthroline, 2 mM; EDTA, 2 mM. The reaction mixtures were incubated in a pH 7.4 phosphate buffer at room temperature for 24 h under ambient air.

damage via site-specific •OH generation. It may also be noted that an earlier study has shown that ascorbate is able to reduce Cr(VI) and Cr(V) to Cr(IV). We have shown that as with Cr(III) and Cr(V), Cr(IV) is also able to generate •OH radicals from H_2O_2 via a Fenton-like reaction [9]. Because Cr(IV) is unstable and difficult to detect in aqueous medium, we have not yet been successful in determining whether $O_2^{\bullet -}$ is able to reduce Cr(V) to Cr(IV). The scheme that summarizes chromium-mediated •OH generation via $O_2^{\bullet -}$-mediated reactions is provided in Fig. 5.

Metal ion chelators, deferoxamine, 1,10-phenanthroline and EDTA, decreased the •OH generation. Among these chelators, deferoxamine and 1,10-phenanthroline are particularly interesting. Deferoxamine is widely used for prevention and treatment of iron overload as well as for combating the toxic effect of vanadium [26–28]. Deferoxamine is also able to decrease •OH generation from H_2O_2 by transition metal ions, Fe(II), V(IV) and Cr(V) [26,27,29]. As for 1,10-phenanthroline, it is a membrane-permeable chelating agent that has been reported to inhibit H_2O_2-induced DNA damage [30], mutation and transformation [31]. This chelator has also been reported to form a complex with transition metal ions, such as iron, to block •OH generation [32]. Recently, 1,10-phenanthroline has been shown to protect cells from either Cr(VI)-mediated alkali-labile sites or the combination of alkali-labile site formation plus DNA damage [33]. This chelator has also been reported to decrease Cr(V) formation during the reduction of Cr(VI) by whole living mice [34]. The results obtained from the present study suggest the hypothesis that metal chelation may be used as a strategy to attenuate Cr(VI)-mediated carcinogenesis via inhibition of •OH radical generation.

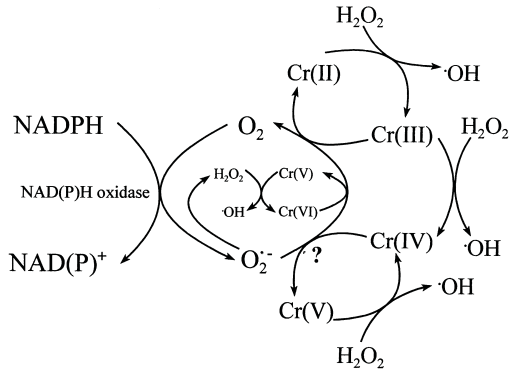

Fig. 5. A scheme of Cr(III)-mediated Haber-Weiss reactions.

In the present study, HPLC with electrochemical detection was used to study the dG hydroxylation by •OH radical generated by Cr(III) through Haber-Weiss reactions. The 8-OHdG formation is considered a marker of DNA damage by •OH generating species [35]. 8-OHdG formation in DNA is known to cause misreplication of DNA that may lead to cell mutation and cancer [35]. It has been reported that the presence of 8-OHdG in a DNA template causes point mutation consisting of G–T transversions [36]. The results obtained from the present study show that •OH radicals generated from Cr(III) can react with dG to form 8-OHdG. It may be noted that •OH radicals generated in the reaction of H_2O_2 with certain metal ions, such as nickel [37], copper or zinc containing superoxide dismutase [38], exhibit very limited reactivity. For example, the •OH radicals generated by these systems cannot be scavenged by ethanol or formate. The reason for this nonreactivity is thought to be that •OH radicals are generated within the domain of certain macromolecules [37,38] and hence are not "free" to exhibit significant reactivity [37–40]. The present study shows that •OH radicals generated by Cr(III) through Haber-Weiss reactions are free and do have the potential to react with dG. This result suggests that •OH radicals generated by Cr(III) reactions can cause DNA damage via an hydroxylation reaction.

In conclusion, the results obtained from the present study demonstrate the following: (a) Cr(III) through Haber-Weiss reactions are free and do have the potential to react with dG. This result suggests that •OH radicals generated by Cr(III) reactions can cause DNA

damage via an hydroxylation reaction. (b) Metal chelators, deferoxamine, 1,10-phenanthroline and EDTA decrease the radical generation. (c) The relative yield of $^{\bullet}OH$ radicals generated by Cr(III) reactions is lower than that generated by Cr(VI)-mediated Haber-Weiss reactions and comparable with that of Fe(II)-mediated reactions. (d) The $^{\bullet}OH$ radicals generated by Cr(III) reactions can cause dG hydroxylation to generate 8-OHdG. (e) Since Cr(III) is able to bind to DNA, Cr(III) may cause DNA damage via a site-specific $^{\bullet}OH$ generation via Haber-Weiss reactions.

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