Peroxynitrite (ONOO⁻), the product of superoxide (O₂⁻) and nitric oxide (NO) reaction, inhibits mitochondrial respiration and can stimulate apoptosis. Cytochrome c, a mediator of these two aspects of mitochondrial function, thus represents an important potential target of ONOO⁻ during conditions involving accelerated rates of oxygen radical and NO generation. Horse heart cytochrome c³⁺ was nitrated by ONOO⁻, as indicated by spectral changes, Western blot analysis, and mass spectrometry. A dose-dependent loss of cytochrome c³⁺ 695 nm absorption occurred, inferring that nitrination of a critical heme-vicinal tyrosine (Tyr-67) promoted a conformational change, displacing the Met-80 heme ligand. Nitrination was confirmed by cross-reactivity with a specific antibody against 3-nitrotyrosine and by increased molecular mass compatible with the addition of a nitro (NO₂) group. Mass analysis of tryptic digests indicated the preferential nitrination of Tyr-67 among the four conserved tyrosine residues in cytochrome c. Cytochrome c³⁺ was more extensively nitrated than cytochrome c²⁺ because of the preferential oxidation of the reduced heme by ONOO⁻. Similar protein nitrination patterns were obtained by ONOO⁻ reaction in the presence of carbon dioxide, whereupon secondary nitrating species arise from the decomposition of the nitrosperoxocarboxylate (ONOOCO₂⁻) intermediate. Peroxynitrite-nitrated cytochrome c displayed significant changes in redox properties, including (a) increased peroxidatic activity, (b) resistance to reduction by ascorbate, and (c) impaired support of state 4-dependent respiration in intact rat heart mitochondria. These results indicate that cytochrome c nitrination may represent both oxidative and signaling events occurring during NO- and ONOO⁻-mediated cell injury.

Cytochrome c is a small globular protein that contains a covalently bound heme located in an internal pocket formed by highly conserved amino acid residues (12–14). The porphyrin in cytochrome c exists in high concentrations in mitochondria (-400 μM) (35) and may also become nitrated during conditions involving accelerated rates of oxygen radical and NO generation. We have previously reported the direct one-electron oxidation of the heme of cytochrome c²⁺ by ONOO⁻ (7 = 2 × 10⁵ M⁻¹ s⁻¹) (36), but modification of the protein moiety induced by NO-derived reactive species has not been studied. In this regard, nitrination of cytochrome c tyrosine residues can have a profound influence on protein structure and function because the inner mitochondrial membrane and participates in mitochondrial electron transport (1–3). The release of cytochrome c from mitochondria to the cytosol via a Bcl-2-inhibitable mechanism constitutes an early event in apoptosis and can occur before changes in mitochondrial membrane potential (4–11). The mechanisms mediating cytochrome c release from mitochondria and how this event triggers apoptosis in the cytosol remain to be defined.

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two tyrosines (Tyr-67 and Tyr-48; Fig. 1) lie adjacent to the critical catalytic environment of the heme pocket. Indeed, early work indicated that exposure to excess amounts of the nitrating and oxidizing compound tetraniitromethane (TNM) resulted in tyrosine nitration and was accompanied by changes in cytochrome c chemical properties and respiratory function (37).

Here we report the nitration of mitochondrial cytochrome c by ONOO\(^{-}\), reveal the influence of this modification on cytochrome c function, and discuss the potential biological relevance of this reaction in the context of oxidant-mediated cell injury.

**EXPERIMENTAL PROCEDURES**

**Chemicals**—Horse heart cytochrome c (catalogue number C-7752), 2,2-azino-bis(3-ethylbenzthiolozine-6-sulfonic acid) diammonium salt (ABTS), diethylenetriaminepentaacetic acid (DTPA), horseradish peroxidase, succinic acid, antimycin A, 3-(N-morpholino)propanesulfonic acid, EGTA, sodium dithionite, and fatty acid-free bovine serum albumin (fraction V) were obtained from Sigma. Sequencing grade-modified trypsin was obtained from Promega. Tetraniitromethane was obtained from Fluka, and hydrogen peroxide was obtained from Baker. All other reagents were of research-grade quality.

A rabbit polyclonal antibody against nitrotyrosine was raised with nitratated keyhole limpet hemocyanin and purified in our laboratory by affinity chromatography as described elsewhere (38). Peroxynitrite was synthesized, quantitated, and handled as described previously (39).

**Cytochrome c Nitration**—In some cases, nitration was performed by reaction of 40 mM tetraniitromethane in 95% ethanol with cytochrome c\(^{2+}\) (1 mM) in 0.1 M Tris-HCl and 0.1 M KCl (pH 8.0) at room temperature for 30 min. The final concentration of ethanol was always less than 6%. The reaction was terminated by passing the mixture through a Sephadex G-25 column in 0.1 M Tris-HCl and 0.1 mM KCl, pH 8.0 (40).

During reaction with ONOO\(^{-}\), cytochrome c in 200 mM potassium phosphate and 100 mM DTPA, pH 7.0, was subjected to bolus addition of ONOO\(^{-}\) at 25 °C. The pH was controlled after each addition and was always kept below pH 7.4. In some experiments, NaHCO\(_3\) (25 mM) was added. Control experiments (reverse order addition experiments) in which ONOO\(^{-}\) was first decomposed in the reaction buffer before the addition of cytochrome c were performed systematically to estimate the potential effects of the byproducts nitrate (NO\(_3\)) and nitrite (NO\(_2\)).

**Biochemical Analyses**—Peroxidatic activity of native or ONOO\(^{-}\)-treated cytochrome c (0.6 μM) in 100 mM potassium phosphate plus 100 μM DTPA, pH 7.2, was assayed with 1.3 mM ABTS and 12 mM H\(_2\)O\(_2\) at 20 °C. ABTS oxidation was followed at 420 nm, ε = 36 mM\(^{-1}\) cm\(^{-1}\) (41).

Mitochondrial respiration was measured polarographically using a Cole-Palmer oxymeter fitted with a water-jacketed Clark-type electrode (YSI Model 5300) in a 1.0-ml reaction vessel. Oxygen consumption studies were performed in mitochondrial homogenization buffer at 37 °C, pH 7.4, using 0.2–0.5 mg/ml mitochondria. Succinate (6 mM) was used to quantitate complex II-dependent respiration (21). All spectrophotometric measurements were performed in a Shimadzu UV-2401 PC spectrophotometer. Protein concentration was determined by the Bradford method (42).

**Electrophoretic Analysis**—Native polyacrylamide gel electrophoresis was performed using 15% polyacrylamide with a 3.5% stacking gel with a 22 mM Tris-glycine, pH 8.3, as the electrolyte buffer. Because cytochrome c has a high isoelectric point, samples were run from anode to cathode. Control-, TNM-, and ONOO\(^{-}\)-treated cytochrome c was also separated by electrophoresis on SDS-15% polyacrylamide gels and analyzed by Western blotting (20 mA, 16 h) to nitrocellulose membranes (pore size, 0.45 μm; Hybrid-C Extra; Amersham). Nonspecific binding sites were blocked for 1 h with 5% bovine serum albumin, 50 mM Tris-HCl, 150 mM NaCl, and 0.6% Tween 20, pH 7.4. Nitrocellulose membranes were probed with rabbit polyclonal antibody against nitrotyrosine (1:1000 dilution) (38) in blocking buffer containing 2% milk IgG. Probed membranes were washed in blocking buffer containing 0.3% Tween 20, and immunoreactive protein was detected by luminol-enhanced chemiluminescence (ECL; Amersham).

**Mitochondrial Preparation**—Intact rat heart mitochondria were prepared by differential centrifugation as described previously (15, 21). Mitochondrial pellets were resuspended in a minimal volume of the homogenization buffer containing 0.3 M sucrose, 5 mM potassium phosphate, 1 mM EGTA, 0.1% bovine serum albumin, pH 8.0, to 25–35 mg protein/ml and kept at 4 °C until use (21). Respiratory control ratio for complex II-dependent respiration typically ranged between 3 and 5. For cytochrome c extraction, mitochondrial pellets were resuspended in 10 mM KCl and 2 mM Tris-HCl, pH 7.4, to a protein concentration of 2 mg/ml and then divided in two fractions, A and B. Samples were incubated for 10 min at 37 °C and then centrifuged at 10,000 × g at 4 °C. The pellet of fraction A was resuspended in the same buffer, whereas pellet B was resuspended in 150 mM KCl and 2 mM Tris-HCl, pH 7.4, to extract cytochrome c (43). Fractions A and B were incubated and centrifuged twice using the same conditions, and supernatants were collected and measured spectrophotometrically after the addition of dithionite. The concentration of cytochrome c\(^{2+}\) was determined by absorbance at 550 nm (ε = 21 mM\(^{-1}\) cm\(^{-1}\)) (43). Typically, 0.6 ± 0.1 mM cytochrome c\(^{2+}\) mitochondrial protein was extracted.

**Tryptic Digestion and Peptide Mapping**—Cytochrome c\(^{2+}\) samples (control and samples treated with peroxynitrite) were exhaustively dialyzed against 100 mM ammonium bicarbonate, pH 8.0, and cleaved with sequencing grade-modified trypsin in a 1:100 ratio (w/w) at 37 °C for 16 h. The peptides were analyzed by a Hewlett Packard HPLC system with a diode array detector using an octadecyl silica gel reverse-
RESULTS

Spectroscopic Analysis of Cytochrome c Nitration—Cytochrome $c^{3+}$ (200 $\mu$M) was exposed to successive additions of 3 $\mu$M NOO$^-$, and spectral changes in the visible region were observed. Peroxynitrite caused a dose-dependent disappearance of the characteristic 695 nm absorbance of native cytochrome $c^{3+}$ at pH 7.0, indicating loss of Met-80-heme iron interactions (Fig. 2; Ref. 14). This spectral change may be due to the nitration of Tyr-67, which promotes the displacement of the characteristic 695 nm absorbance of native cytochrome $c^{3+}$ at pH 7.0, indicating loss of Met-80-heme iron interactions (Fig. 2; Ref. 14). This spectral change may be due to the nitration of Tyr-67, which promotes the displacement of Met-80 from its coordination bond at the Fe atom (45, 46).

Because yields of phenolic nitration by NOO$^-$ usually increase in the presence of CO$_2$ through the intermediate formation of nitrosperoxocarboxylate (ONOOCO$_2$), a comparative study of the spectral changes of cytochrome $c$ mediated by ONOO$^-$, with and without CO$_2$ and TNM exposure, was performed (Fig. 3). Peroxynitrite at a cumulative dose of 18 $\mu$M caused a similar decrease in the 695 nm band with or without CO$_2$, whereas TNM (40 $\mu$M) led to more pronounced but comparable spectral changes (Fig. 3A). We next analyzed the 605–615 nm absorbance of cytochrome $c$, in which TNM reaction with cytochrome $c$ reveals a characteristic shoulder (45). In this region, the reaction of NOO$^-$ yielded an effect similar to that of TNM in both the presence and absence of CO$_2$ (Fig. 3B). Finally, a blue shift of 2–3 nm in the Soret band was observed after all three nitrating reactions (Fig. 3C). A moderate loss of Soret absorption was observed, especially in the case of TNM, indicating that at high concentrations (40 $\mu$M), there may have been some opening of the heme. In contrast, similar concentrations of H$_2$O$_2$ led to total heme loss (41, 50).

In native cytochrome $c^{3+}$, the 695 nm band has a $pK_a$ of 9.5 because of the conformational transition between states III and IV, which involves the substitution of the Met-80 from the heme, presumably by Lys-79 (14). After the TNM reaction, the $pK_a$ of the transition decreases to 6.5 because the nitration of Tyr-67 causes $pK_a$ lowering (45) and affects the liganding tendency of Lys-79 to the heme iron. The lost 695 nm band in cytochrome $c$ after ONOO$^-$ treatment at neutral pH was partially recovered at an acidic pH (i.e., pH 5) but not at an alkaline pH (i.e., pH 8.8; data not shown), resembling the effect of TNM and further suggesting the nitration of Tyr-67.
Fig. 4. Anti-nitrotyrosine immunoblotting of cytochrome c. Cytochrome c (250 μm) was incubated in 100 mM potassium phosphate, pH 7.2, at 25 °C with ONOO− and then separated on a SDS-15% polyacrylamide gel and examined by Western blot analysis with a polyclonal antibody against nitrotyrosine as described under “Experimental Procedures. Lane 1, 1 μm bovine serum albumin; lane 2, control cytochrome c; lanes 3–5, cytochrome c treated with 0.5, 1, and 2 mM ONOO−, respectively. Lanes 6–9 are as described for lanes 2–5 but using cytochrome c instead of cytochrome c3+. Lane 10 corresponds to 1 μm nitrated bovine serum albumin.

**Electrophoretic Analysis of Native and Nitrated Cytochrome c**—The addition of ONOO− to cytochrome c results in protein nitration, as revealed by reactivity with anti-nitrotyrosine antibody. Extents of nitration by ONOO− were dose-dependent. Importantly, the oxidized form of cytochrome c (cytochrome c3+) was more extensively nitrated than the reduced form (cytochrome c$^{2+}$), supporting a preferential reaction between reduced heme and ONOO− (36) (Fig. 4). At greater concentrations of ONOO−, a second nitrated band of approximately 24 kDa appears, compatible with the formation of dimerized cytochrome c, similar to hemoglobin nitration by ONOO− (51). Tetranitromethane-treated cytochrome c also had cross-reactivity with the anti-nitrotyrosine antibody (data not shown).

Native gel electrophoresis shows that ONOO− causes a dose-dependent appearance of up to three species, displaying decreased migration toward the cathode (Fig. 5), whereas native cytochrome c progressively diminished in staining intensity. The electrophoretic properties of these novel cytochrome c species infer a decreased isoelectric point compatible with the formation of nitrotyrosine residues and a consequent lowering of pKa (52), as observed previously during ONOO−-mediated nitration of bovine CuZn-SOD (53). Similar products were observed when ONOO− was added to cytochrome c in the presence of CO2. High concentrations of TNM (40 mM) yielded a band pattern similar to that observed with ONOO−, plus an additional fifth band close to the anode (Fig. 5, lane 9).

**Mass Spectrometry Studies and HPLC Analysis of Tryptic Digests**—Exposure of cytochrome c3+ (200 μm) to 0.5 mM ONOO− resulted in a 46-Da increase in the mass (12,356 to 12,402 Da; Fig. 6B) of ~20% of the parent protein. This is consistent with the addition of one nitro group (45 Da) per molecule of cytochrome c. At 2 mM ONOO−, there was a further increase in the 12,402 Da species (from 20% to 28%), plus the appearance of a new species (8%) of increased molecular mass of 91 Da (12,447 Da) with respect to the parent protein, indicating the addition of two nitro groups to a small fraction of the protein (Fig. 6C). At a cumulative dose of 18 mM ONOO−, the 12,447 Da (i.e. containing two 3-nitrotyrosine residues) species was predominant, and other molecular mass species were detected as well, in particular, (a) a component in the region of 12,491 Da compatible with the addition of a third nitro group, and (b) a component of 12,415 compatible with the addition of one nitro group and one oxygen (data not shown). Similarly, cytochrome c3+ treatment with 40 mM TNM resulted in the formation of three main species, consistent with mononitrated, dinitrated, and, to a lesser extent, trinitrated forms of the protein (data not shown).

The reverse-phase HPLC elution profile of peptides generated by tryptic digestion of cytochrome c after treatment with 18 mM ONOO− (Fig. 7B) was compared with native cytochrome c (Fig. 7A). The same chromatographic profile was obtained with cytochrome c3+ after treatment with TNM (data not shown). To identify the site(s) of nitration, tryptic peptides of ONOO−-treated cytochrome c having absorbance at 365 nm were collected and subjected to mass spectrometric analysis. The peptide eluting at 32 min (the first asterisk in Fig. 7B) had a molecular mass of 1516.2 Da, corresponding to the tryptic

**Fig. 6.** Mass spectrometry of native (A) and peroxynitrite-modified (B) cytochrome c3+. Deconvolution masses of cytochrome c control (A) and cytochrome c (200 μm) reacted with 0.5 mM (B) and 2 mM (C) peroxynitrite in the presence of 25 mM bicarbonate.
fragment T^{40}GQAPGFTY^{48}TDANK^{53} plus 45 Da (the untreated peptide molecular mass was 1470.68 Da). Mass spectrometric analysis of the peptide eluting at 42.4 min (the second asterisk in Fig. 7B) revealed a molecular mass of 1540.8 Da, corresponding to the tryptic fragment E^{53}ETLMEY^{67}L-ENPK^{52} plus 45 Da. The expected mass of the control fragment was 1495.7 Da. The increase in mass by 45 Da in both peptides indicated the nitration of residues Tyr-48 and Tyr-67. Cytochrome c^{3+} treated with a 10-fold excess of ONOO\(^{-}\) showed the same peak at 42.4 min and the same mass of the peptide but did not include a peptide eluting at 32 min. Thus, at lower ONOO\(^{-}\) concentrations, only nitration of Tyr-67 is observed, whereas at higher concentrations of ONOO\(^{-}\), Tyr-67 and Tyr-48 are nitrated. Although mass spectrometric analysis of cytochrome c exposed to 40 mM TNM or 18 mM ONOO\(^{-}\) showed an increase in mass suggestive of nitration of three tyrosine residues, a third nitrated tyrosine was not apparent after tryptic digestion and HPLC-mass spectrometry analysis. Sokolovsky et al. (37) reported nitration of Tyr-47 and Tyr-48 after exposure to a 60-fold excess of TNM. They also reported a small amount of nitrated residue Tyr-74 (37). It is possible that the third nitrated tyrosine (Tyr-74) was not detected after tryptic digestion and HPLC-mass spectrometry analysis because of the low yield of nitration of this residue and/or the small size of the tryptic fragment (723.4 Da) where Tyr-74 is located. Changes in Cytochrome c Redox and Catalytic Properties—Cytochrome c^{3+} induces ABTS oxidation in the presence of H\(_2\)O\(_2\), with this catalytic activity of cytochrome c increased by preincubation with H\(_2\)O\(_2\) (41). Peroxynitrite-treated cytochrome c^{3+} was also a better catalyst of ABTS oxidation than native cytochrome c (Fig. 8), increasing the rate of ABTS oxidation in a dose-dependent manner. The activation of this peroxidase activity of cytochrome c is related to nitration. In the absence of electron donors such as ABTS, cytochrome c^{3+} treated with ONOO\(^{-}\) and TNM becomes more sensitive to H\(_2\)O\(_2\)-mediated inactivation, as evidenced by the facile loss of the Soret absorption band (Fig. 8, inset). This supports the concept that nitration of Tyr-67 promotes a displacement of the sixth ligand position of the heme, favoring the interaction with H\(_2\)O\(_2\) and oxidative degradation of the heme via formation of oxo-iron complexes (i.e., ferriy iron) (41). Finally, nitrated cytochrome c^{3+} was resistant to reduction by ascorbate (Fig. 9). Mitochondrial Respiration after Nitration of Cytochrome c—Intact rat heart mitochondrial respiration was studied in the presence of native and ONOO\(^{-}\)-nitrated cytochrome c^{3+}. State 4 mitochondrial respiration was inhibited 70% upon cytochrome c extraction (Fig. 10, A and B), affirming the essential role of cytochrome c in electron transport (2, 3). Supplementation of cytochrome c-depleted mitochondria with native cytochrome c^{3+} restored oxygen consumption rates to control values (Fig. 10B). Re-supplementation of mitochondria with ONOO\(^{-}\)-treated cytochrome c restored less than 50% respiration rates (Fig. 10C). It is important to note that the treatment for nitration used here (six bolus additions of 1 mM ONOO\(^{-}\) to 200 mM cytochrome c^{3+}) led to nitration of Tyr-67 (Figs. 6 and 7), but also left a significant fraction of native cytochrome c^{3+} as well (Figs. 5 and 6), the latter being the main one, responsible for the partial recovery of respiration (Fig. 10C). Similar results were obtained with cytochrome c nitratd by TNM exposure (data not shown), in line with previous results (45). DISCUSSION Peroxynitrite is capable of nitrating cytochrome c^{3+}, as demonstrated by Western blot analysis and mass spectrometry studies. The nitrating capability of ONOO\(^{-}\) was comparable to that of TNM. Cytochrome c^{3+} reaction with ONOO\(^{-}\) led to changes in spectral properties, most notably the disappearance of the absorption band at 695 nm, indicating that Met-80 ceases to coordinate with the Fe atom. This could be due to nitration of the nearby tyrosine residue Tyr-67 (45), but additional or alternative mechanisms such as Met-80 oxidation or modifica-
Cytochrome c Nitration

Fig. 9. Resistance to reduction by ascorbate of nitrated cytochrome c. Native cytochrome c\(^{3+}\) (solid line), cytochrome c\(^{3+}\) treated with 40 mM TNM (dotted line), and cytochrome c\(^{3+}\) treated with six bolus additions of 3 mM ONOO\(^{-}\) (dashed line) were incubated at a concentration of 10 \(\mu\)M for 60 min in the presence of 50 \(\mu\)M ascorbate in 200 mM potassium phosphate plus 100 \(\mu\)M DTPA at 20 °C, pH 7.2, and absorbance changes at 550 nm were followed.

![Graph showing resistance to reduction by ascorbate of nitrated cytochrome c](image)

Fig. 10. Mitochondrial oxygen consumption in the presence of nitrated cytochrome c. State 4 oxygen consumption in presence of succinate was studied in intact rat heart mitochondria (0.5 mg/ml). Respiration of control mitochondria (A) and cytochrome c-depleted mitochondria followed by supplementation with 0.7 mmol/mg native (B) or ONOO\(^{-}\)-treated cytochrome c (C), is shown. The reaction vessel contained 1.6 ml of final reaction volume.

![Diagram showing mitochondrial oxygen consumption in the presence of nitrated cytochrome c](image)

The biological relevance of these findings remains to be defined. First, cytochrome c\(^{3+}\) nitration yields by ONOO\(^{-}\) were not high because 0.5 mM ONOO\(^{-}\) nitrated ~20% of 200 \(\mu\)M cytochrome c\(^{3+}\) (i.e. ~40 \(\mu\)M; Fig. 6B), implying ~8% yield. Secondly, nitration of cytochrome c\(^{3+}\) was attenuated due to preferential oxidation of the heme (36). Interestingly, cytochrome c nitration occurred in the presence of CO\(_2\) which is abundant in mitochondria and a catalyst of the intermediate formation of the nitrating species ONOO\(^{-}\). However, the possibility that cytochrome c\(^{3+}\) nitration would significantly impair mitochondrial respiration is remote in light of the high amounts of ONOO\(^{-}\) required and the recognition that other more oxidant-sensitive electron transport components would be inactivated at lower ONOO\(^{-}\) concentrations (15, 21). On the other hand, small quantities of nitrated cytochrome c\(^{3+}\) could mediate signaling reactions and/or serve as a footprint during NO\(^{-}\)- and ONOO\(^{-}\)-mediated injury and apoptotic processes, which involve cytochrome c\(^{3+}\) release to the cytosol. Indeed, despite the various potential intramitochondrial protein targets susceptible of nitration, current work reveals that biologically relevant concentrations of ONOO\(^{-}\) cause cytochrome c nitration\(^{-}\) and release (11) in intact mitochondria. Moreover, nitrated cytochrome c may be released to the cytosol in cells exposed to NO\(^{-}\) (56), although the correlation between apoptotic cell death and cytochrome c nitration requires further investigation.

In various pathophysiological situations, mitochondrial ONOO\(^{-}\) formation occurs readily due to the increased formation of O\(_2\) by the respiratory chain and the presence of enhanced NO synthesis in extramitochondrial or possibly intramitochondrial sites (57–59). Thus, cytochrome c\(^{3+}\) could be nitrated by mitochondrial but also cytosolic or extracellular-derived ONOO\(^{-}\) diffusing to the intermembrane space. In summary, we report that peroxynitrite can mediate the nitration and functional modification of cytochrome c, a critical component of respiratory and apoptotic signaling reactions.

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\(^2\) A. Cassina and R. Radi, unpublished observations.
Cytochrome c Nitration by Peroxynitrite
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