p-Hydroxyphenylacetaldehyde Is the Major Product of l-Tyrosine Oxidation by Activated Human Phagocytes

A CHLORIDE-DEPENDENT MECHANISM FOR THE CONVERSION OF FREE AMINO ACIDS INTO REACTIVE ALDEHYDES BY MYELOPEROXIDASE*

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Stanley L. Hazen, Fong Fu Hsu, and Jay W. Heinecke†
From the Departments of Medicine and Molecular Biology and Pharmacology, Washington University School of Medicine, St. Louis, Missouri 63110

Reactive aldehydes generated during lipid peroxidation have been implicated in the pathogenesis of atherosclerosis as well as other inflammatory diseases. A potential catalyst for such reactions is myeloperoxidase, a hemeprotein secreted by activated phagocytes. We now report that activated neutrophils utilize the myeloperoxidase-H$_2$O$_2$-chloride system to convert l-tyrosine to p-hydroxyphenylacetaldehyde. Production of p-hydroxyphenylacetaldehyde was nearly quantitative at physiological concentrations of l-tyrosine and chloride. Aldehyde generation required myeloperoxidase, H$_2$O$_2$, l-tyrosine, and chloride ion; it was inhibited by the H$_2$O$_2$ scavenger catalase and by the heme poisons azide and cyanide. Phorbol ester- and calcium ionophore-stimulated human neutrophils likewise generated p-hydroxyphenylacetaldehyde from l-tyrosine by a pathway inhibited by azide, cyanide, and catalase. Aldehyde production accounted for 75% of H$_2$O$_2$ generated by optimally stimulated neutrophils at plasma concentrations of l-tyrosine and chloride. Collectively, these results indicate that activated phagocytes, under physiological conditions, utilize myeloperoxidase to execute the chloride-dependent conversion of l-tyrosine to the lipid-soluble aldehyde, p-hydroxyphenylacetaldehyde, in near quantitative yield. Moreover, like aldehydes derived from lipid peroxidation, amino acid-derived aldehydes may exert potent biological effects in vascular lesions and other sites of inflammation.

Covalent modification of proteins by reactive aldehydes has been implicated in the pathogenesis of conditions ranging from aging to atherosclerosis and diabetic vascular disease (1–5). The pathways that promote aldehyde formation in vivo, as well as the precise chemical identity of these oxidizing intermediates, remain poorly understood. One mechanism at sites of inflammation may involve myeloperoxidase, a hemeprotein secreted by phagocytic white blood cells (6–8). Phagocyte activation triggers a membrane-associated NADPH oxidase to reduce oxygen to superoxide anion (O$_2^-$) (9), which subsequently dismutates to form hydrogen peroxide (H$_2$O$_2$). H$_2$O$_2$ is then used as an oxidizing substrate by myeloperoxidase to generate bacteriocidal and cytotoxic compounds (6–8).

The best characterized product of myeloperoxidase at plasma concentrations of chloride ion is hypochlorous acid (HOCl) (10, 11):

\[
\text{Cl}^- + \text{H}^+ + \text{H}_2\text{O}_2 \rightarrow \text{HOCl} + \text{H}_2\text{O}
\]

REACTION 1

This potent oxidant bleaches hemeproteins (12), converts unsaturated lipids to chlorohydrins (13, 14), and reacts with amino groups to form chloramines (15, 16). Proteins exposed to reagent HOCl undergo aggregation with the concomitant formation of moieties that react with carbonyl-derivating agents, suggesting the formation of reactive aldehydes and/or ketones (17–20). Indirect evidence suggests that free amino acids may also serve as targets for oxidation by myeloperoxidase to generate reactive carbonyl groups (21, 22). High concentrations of reagent HOCl react with l-tyrosine at pH 3 to yield trace amounts of chlorotyrosine-derived aldehydes (23), but the physiological significance of this reaction has not been investigated. Neither the reaction pathways nor the structures of the products generated in these reactions have been clearly established.

We have shown that l-tyrosine is a substrate for oxidation by phagocyte-derived myeloperoxidase (24, 25). The major product of this reaction in the absence of chloride ion is tyrosyl radical (24–26), which then undergoes a radical coupling reaction to form o,o'-dityrosine (27–29). Because chloride is present at high concentrations in vivo and has been shown to inhibit o,o'-dityrosine synthesis (24, 25), we investigated whether other l-tyrosine oxidation products might be generated at physiological concentrations of chloride. We now report that activated human neutrophils utilize the myeloperoxidase-H$_2$O$_2$-chloride system to synthesize an amphipathic l-tyrosine oxidation product in near quantitative yield. We have characterized this novel lipid-soluble product and show that it is p-hydroxyphenylacetaldehyde. Our observations raise the possibility that myeloperoxidase converts plasma amino acids into freely diffusible aldehydes, which may then react with critical molecular targets at sites of inflammation.

**EXPERIMENTAL PROCEDURES**

**Materials**

Sodium phosphate, ethyl acetate, H$_2$O$_2$, and sodium hypochlorite were obtained from Fisher, Boehringer Mannheim provided Chelex 100 resin and crystalline catalase (from bovine liver, thymol-free). Deuterated methand and chloroform were from Cambridge Isotopes, Inc.
HPLC solvents were purchased from Baxter. All other materials were purchased from Sigma except where indicated.

Methods

Isolation of Myeloperoxidase—Myeloperoxidase was extracted with cetyltrimethylammonium bromide from human leukocytes obtained by leukopheresis (30). Solubilized myeloperoxidase was purified by lectin affinity chromatography and size-exclusion chromatography (Superose 6 column; Pharmacia Biotech Inc.) as described previously (24, 30). Enzyme was dialyzed against H2O and stored in 50% glycerol at −20°C. Myeloperoxidase prepared by this method had an A280 nm/Abat ratio of 0.6. Enzyme concentration was determined spectrophotometrically (ε280 = 170 mM−1 cm−1) (31).

Isolation of Human Neutrophils—Neutrophils were isolated by buoyant density centrifugation. Blood (25 ml) anticoagulated with EDTA (final concentration of 5.4 mM) was layered over Polymorph-Prep (25 ml; Nycomed, Sunnyvale, CA) in a 50-ml polypropylene centrifuge tube and then subjected to centrifugation at 500 × gmax for 30 min at 20°C. The polymorphonuclear leukocyte fraction was isolated; an equal volume of medium A (Hanks’ balanced salt solution (magnesium-, calcium-, phenol-, and bicarbonate-free; Life Technologies, Inc.) supplemented with 100 μM DTPA, pH 7.20) that had been diluted with water (1:1, v/v) was added; and the cells were washed twice with medium A by centrifugation. Residual red blood cells were removed by hypotonic lysis at 4°C. Neutrophils were pelleted by centrifugation, resuspended in medium A, and immediately used for experiments.

p-Hydroxyphenylacetaldehyde Production—Quantitative determination of p-hydroxyphenylacetaldehyde production was performed utilizing reverse-phase HPLC with a C18 column (Beckman UltraspHERE ODS, 5 μm, 4.6 × 250 mm) equilibrated with solvent A (5% methanol, 0.1% trifluoroacetic acid, pH 2.5). L-Tyrosine and its oxidation products were eluted at a flow rate of 1 ml/min with a nonlinear gradient generated with solvent B (90% methanol, 0.1% trifluoroacetic acid, pH 2.5): 0–35% solvent B over 10 min, isocratic elution at 35% solvent B for 4 min, and 35–100% solvent B over 5 min. Preliminary experiments utilizing L-[3H]tyrosine (DuPont NEN) for the determination of p-[3H]hydroxyphenylacetaldehyde revealed that the ultraviolet absorption spectra and extinction coefficients of tyrosine and the aldehyde were nearly identical at pH 2.5. We therefore routinely quantified p-hydroxyphenylacetaldehyde by integration of peak absorbance monitored at 276 nm employing a standard curve constructed with l-tyrosine. Reactions employing purified myeloperoxidase (0.5–1.0 ml) were allowed to continue to completion (30 min at 37°C) and then directly analyzed by HPLC following injection of reaction mixture (100 μl). Time course experiments with purified myeloperoxidase were terminated by three sequential extractions with ethyl acetate (2 ml each). The combined organic extracts were brought to near dryness under a stream of anhydrous N2, immediately resolubilized in 5% methanol, and then analyzed by reverse-phase HPLC. Addition of HPLC-purified p- [3H]hydroxyphenylacetaldehyde to the reaction mixture prior to analysis demonstrated that the recovery of aldehyde with this procedure was >95%. Preliminary experiments with human neutrophils revealed that 90–95% of the p-hydroxyphenylacetaldehyde partitioned into the cell pellet and was recovered following three sequential extractions with ethyl acetate. We therefore routinely quantified total p-hydroxyphenylacetaldehyde production from human neutrophils by organic solvent extraction of reaction mixtures as described above.

Superoxide Anion Production—Superoxide generation by activated human neutrophils was measured in medium A as the superoxide dismutase-inhibitable reduction of ferricytochrome c (9, 32). Conditions were identical to those employed for measuring p-hydroxyphenylacetaldehyde production except that l-tyrosine was omitted and cytochrome c (1 mg/ml) was included in medium A. Superoxide-specific reduction of cytochrome c was determined spectrophotometrically (ε550 = 21.3 mM−1 cm−1) (33) using cells incubated with or without superoxide dismutase (10 μM/ml).

Instrumentation—Infrared spectra were obtained with a Perkin-Elmer 1760 spectrophotometer. For NMR studies, HPLC-purified p-hydroxyphenylacetaldehyde was extracted into ethyl acetate, brought to near dryness under anhydrous N2, and then repeatedly acetylated with CD3OD to remove exchangeable protons. The aldehyde was resuspended in D2O, and 1H NMR spectroscopy was performed on a Varian Unity 500 spectrometer equipped with a Technivert Vector 1 data system. Gas chromatographic separations were carried out utilizing a 12-m BP-1 capillary column (0.2 mm, inner diameter, 0.33-μm film thickness; Hewlett-Packard) in the splitless mode with helium as the carrier gas. The column was run with the following temperature gradient: 60°C for 1 min; ramped to 120°C at 60°C/min; and ramped to 220°C at 10°C/min. The injector, transfer line, and source temperatures were all set at 240°C. Mass spectra were obtained in the electron impact mode with an electron ionization energy of 70 eV. High resolution electron impact mass spectrometry was performed on a VG-ZAB SE double-focusing mass spectrometer equipped with a VAX Opus 3.1 data system. The resolution was set at 10,000 with perfluorokerosene as the reference. Other Procedures—All buffers (other than those utilized for neutrophil experiments) were Chelex 100-treated. o,o′-Dityrosine production was quantitated by reverse-phase HPLC using the elution conditions for p-hydroxyphenylacetaldehyde. o,o′-Dityrosine was monitored both spectrophotometrically (A276 nm) and by fluorescence (λex = 325 nm; λem = 410 nm) (24, 29). The final concentration of o,o′-dityrosine was calculated from calibration curves constructed utilizing authentic o,o′-dityrosine prepared as described previously (24, 34). Tollen’s test and 2,4-dinitrophenylhydrazine derivatization were performed using standard techniques (35). Protein content was measured by the method of Lowry et al. (36) with bovine serum albumin as the standard.

RESULTS

Myeloperoxidase Converts L-Tyrosine to p-Hydroxyphenylacetaldehyde by a Reaction Requiring H2O2 and Chloride—Addition of purified myeloperoxidase and H2O2 to reaction buffer supplemented with l-tyrosine and plasma concentrations of sodium chloride (100 mM) generated a new species with an ultraviolet absorption maximum and extinction coefficient indistinguishable from those of l-tyrosine. The chloride-dependent oxidation product generated by myeloperoxidase required significantly more methanol than l-tyrosine to elute from a reverse-phase HPLC column (Fig. 1); it also failed to interact with both anion- and cation-exchange columns and

1 The abbreviations used are: HPLC, high performance liquid chromatography; DTPA, diethylene-triaminepentaacetic acid.
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The facile loss of CHO seen with aliphaticaldehydes (M 1 2)

with its chromatographic behavior on C18 and ion-exchange.

L-tyrosine by myeloperoxidase results in loss of both of its

and the L-tyrosine oxidation product (Fig. 2, a and b, respectively) demonstrated the loss of N–H stretch and bend frequencies as well as carboxylic acid O–H stretch frequencies. Furthermore, both C–H and carbonyl stretch frequencies, which are characteristic of aldehydes, were seen in the oxidation product (Fig. 2b). The apparent loss of the polar carboxylate and primary amino groups in the L-tyrosine is consistent with its chromatographic behavior on C18 and ion-exchange matrices as well as its preferential partitioning into organic solvents. These results strongly suggest that oxidation of L-tyrosine by myeloperoxidase results in loss of both of its charged moieties and gain of an aldehyde functional group(s).

The exact mass of the L-tyrosine oxidation product was determined utilizing high resolution mass spectrometry. The mass/charge ratio (m/z) of the molecular ion (M⁺) was 136.0525 (Fig. 3) and is in excellent agreement with an elemental composition of C₈H₈O₂ (m/z 136.0524). The elemental composition, combined with analysis of the Fourier transform IR spectrum, established a preliminary structural assignment of the oxidation product as p-hydroxyphenylacetaldehyde. The proposed structure is strongly supported by the fragmentation pattern of the molecule. The major fragment ion at m/z 107.0501 (C₅H₄O; calculated m/z 107.0496) is consistent with the facile loss of CHO seen with aliphatic aldehydes (M⁺ – 29).

Electron impact mass spectroscopic analysis of the trimethylsilyl-derivated L-tyrosine oxidation product also supported the structural assignment of p-hydroxyphenylacetaldehyde. The trimethylsilyl derivative of the oxidation product yielded the anticipated M⁺ of m/z 208 and fragment ions at m/z 193 (M⁺ – CH₃) and m/z 179 (M⁺ – CHO) (data not shown). High resolution ¹H nuclear magnetic resonance spectroscopy was employed to confirm the chemical identity of the L-tyrosine oxidation product generated by the myeloperoxidase-H₂O₂-chloride system was analyzed by Fourier transform IR spectroscopy as described under “Methods.” Note that the oxidation product has lost the characteristic bending and stretching frequencies associated with the carboxylic acid and amino groups of L-tyrosine (compare A with B) and gained aldehyde C–H and carboxyl stretch frequencies (B).

![Fourier transform infrared spectra of L-tyrosine (A) and p-hydroxyphenylacetaldehyde (B).](image)

FIG. 2. Fourier transform infrared spectra of L-tyrosine (A) and p-hydroxyphenylacetaldehyde (B). The L-tyrosine oxidation product generated by the myeloperoxidase-H₂O₂-chloride system was analyzed by Fourier transform IR spectroscopy as described under “Methods.” Note that the oxidation product has lost the characteristic bend and stretch frequencies associated with the carboxylic acid and amino groups of L-tyrosine (compare A with B) and gained aldehyde C–H and carboxyl stretch frequencies (B).
Synthesis of the amino acid-derived aldehyde demonstrated an absolute requirement for the presence of each of the components of the complete system and was inhibited by the H₂O₂ scavenger catalase. Furthermore, addition of either sodium azide or sodium cyanide, two hemeprotein inhibitors, resulted in complete ablation of aldehyde generation, consistent with a peroxidase-dependent mechanism. Addition of physiological concentrations (and where H₂O₂ was limiting), the yield of aldehyde decreased, consistent with the competing bimolecular mechanism of o,o′-dityrosine formation. Examination of the H₂O₂ concentration dependence for p-hydroxyphenylacetaldehyde (pHPAA) generation revealed that under conditions where L-tyrosine is not limiting, the oxidant is utilized quantitatively for aldehyde generation (Fig. 5).

We have previously shown that myeloperoxidase generates o,o′-dityrosine through a tyrosyl radical-dependent mechanism and that chloride ion inhibits both the yield and rate of L-tyrosine oxidation as assessed by o,o′-dityrosine synthesis (24, 25). We therefore characterized the effect of varying concentrations of chloride on the synthesis of both o,o′-dityrosine and p-hydroxyphenylacetaldehyde. In the absence of chloride, the major L-tyrosine oxidation product generated by the myeloperoxidase-H₂O₂ system was o,o′-dityrosine (Fig. 6). Addition of chloride to the reaction mixture resulted in the concentration-dependent production of p-hydroxyphenylacetaldehyde with the concomitant attenuation of o,o′-dityrosine synthesis (Fig. 6). These results demonstrate that at plasma concentrations of chloride and L-tyrosine (38), myeloperoxidase activation is antici-

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Addition of superoxide dismutase to the reaction mixture, which accelerates the conversion of O$_2^-$ to H$_2$O$_2$; 30fold increase in the yield of aldehyde (Table II). Furthermore, addition of the calcium ionophore ionomycin resulted in further augmentation of aldehyde production (Fig. 7, right panel). Assuming that 2 mol of O$_2^-$ generate 1 mol of H$_2$O$_2$ and that 1 mol of H$_2$O$_2$ is required to oxidize 1 mol of L-tyrosine to generate p-hydroxyphenylacetaldehyde, 30% of the H$_2$O$_2$ derived from O$_2^-$ was used for aldehyde production. Addition of superoxide dismutase to the reaction mixture caused a marked increase in the yield of p-hydroxyphenylacetaldehyde such that ~65% of the O$_2^-$ was employed to generate the aldehyde. Stimulation of the phagocytes with both ionomycin and phorbol myristate acetate augmented O$_2^-$ generation as well as p-hydroxyphenylacetaldehyde synthesis. Under these conditions, ~75% of the O$_2^-$ generated by activated neutrophils was consumed in the chloride-dependent oxidation of L-tyrosine, yielding p-hydroxyphenylacetaldehyde.

**DISCUSSION**

Oxidation of proteins and amino acids by leukocyte-derived HOCl has been intensely studied (17-21); however, the molecular basis underlying the formation of reactive carboxyls has not previously been defined. Our results provide unambiguous evidence that activated human neutrophils employ the myeloperoxidase-H$_2$O$_2$-chloride system to catalyze the conversion of L-tyrosine to p-hydroxyphenylacetaldehyde (Scheme 1).
remarkable feature of this reaction is its nearly quantitative yield. At neutral pH and plasma concentrations of l-tyrosine and chloride, >90% of the H$_2$O$_2$ in the reaction mixture was utilized by purified myeloperoxidase for generation of p-hydroxyphenylacetaldehyde. l-Tyrosine oxidation by activated human neutrophils was also facile; -75% of the O$_2$ generated by optimally stimulated human neutrophils was used for aldehyde synthesis. The chloride dependence of the reaction, as well as the ability of reagent HOCl to execute the same reaction, strongly implicates HOCl (or perhaps enzyme-bound hypochlorite) (41, 42) as the oxidizing intermediate. Indeed, lactoperoxidase and horseradish peroxidase, which do not effectively utilize chloride as a substrate (10), failed to generate p-hydroxyphenylacetaldehyde. Although we have not addressed directly the reaction mechanism for aldehyde generation, it likely involves initial chlorination of the a-amino group (15, 16). Dehydrohalogenation may then yield an imino group. Studies with aliphatic amino acids oxidized by ionizing radiation demonstrate that the imino group is unstable and undergoes spontaneous loss of nitrogen and carbon dioxide, yielding the a-carbon aldehyde derivative of the amino acid (43).

Protein amino and sulfhydryl groups are the major targets for covalent modification by aldehydes (1, 4, 44). These reactions generally proceed via the formation of a Schiff base, which may then undergo further cross-linking reactions. Since aldehydes are restricted in their reactivity and are relatively long-lived, taking hours to reach equilibrium via Schiff base formation (1, 4), they may selectively damage specific cellular targets. The physical properties of p-hydroxyphenylacetaldehyde are particularly well suited for mediating such damage. Although p-hydroxyphenylacetaldehyde is soluble in aqueous solutions, where both the polar phenolic and aldehyde groups facilitate solvation, it was found to preferentially partition into the lipid fraction of neutrophils. Thus, generation of p-hydroxyphenylacetaldehyde by activated human neutrophils results in the generation of a selectively reactive amphiphatic compound, which may partition into or through lipid membranes. The aldehyde should thus readily diffuse from its aqueous site of generation to both intramembranous and intracellular targets, where locally high concentrations may then develop.

Our results suggest that the generation of amino acid-derived aldehydes by activated phagocytes represents another potential mechanism for the covalent modification of proteins. Such aldehydes might react with amino groups on proteins, generating Schiff base adducts by a pathway independent of reducing sugars (4) and lipid peroxidation (1, 3, 5, 44). It is noteworthy that in plasma the total concentration of amino acids ranges from 2 to 4 mM (38) and that every other common amino acid except proline possesses an a-amino group. The conversion of l-tyrosine to p-hydroxyphenylacetaldehyde by myeloperoxidase is nearly quantitative, suggesting that other amino acids may undergo similar reactions. Thus, under conditions where myeloperoxidase is exposed to physiological concentrations of amino acids and chloride, low molecular weight, freely diffusible aldehydes may be the major products of phagocyte activation. Moreover, the conversion of l-tyrosine or other amino acids to reactive aldehydes by myeloperoxidase may constitute an important mechanism for the selective damage of critical targets in inflammation and vascular disease (1-5, 44).

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