Catalytic Consumption of Nitric Oxide by Prostaglandin H Synthase-1 Regulates Platelet Function*

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Nitric oxide (NO) plays a central role in vascular homeostasis via regulation of smooth muscle relaxation and platelet aggregation. Although mechanisms for NO formation are well known, removal pathways are less well characterized, particularly in cells that respond to NO through activation of soluble guanylate cyclase. Herein, we report that NO is catalytically consumed by prostaglandin H synthase-1 (PGHS-1) through acting as a reducing peroxidase substrate. With purified ovine PGHS-1, NO consumption requires peroxide (LOOH or H2O2), with a Km(app) for 15(S)hydroperoxyeicosatetraenoic acid (HPETE) of 3.27 ± 0.35 μM. During this, 2 mol NO are consumed per mol HPETE, and loss of HPETE hydroperoxy group occurs with retention of the conjugated diene spectrum. Hydroperoxide-stimulated NO consumption requires heme incorporation, is not inhibited by indomethacin, and is further stimulated by the reducing peroxidase substrate, phenol. PGHS-1-dependent NO consumption also occurs during arachidonate, thrombin, or A23187 activation of platelets (1-2 μM·min⁻¹ for typical plasma platelet concentrations) and prevents NO stimulation of platelet soluble guanylate cyclase. Platelet sensitivity to NO as an inhibitor of aggregation is greater using a platelet-activating stimulus (U46619) that does not cause NO consumption, indicating that this mechanism overcomes the anti-aggregatory effects of NO. Catalytic consumption of NO during eicosanoid synthesis thus represents both a novel pro-aggregatory function for PGHS-1 and a regulated mechanism for vascular NO removal.

In the vasculature, strict control of nitric oxide (‘NO) bioactivity is essential for both maintaining vascular tone and inhibiting platelet aggregation. Reaction with oxyhemoglobin (oxyHb)³ is generally viewed to be the major fate of ‘NO generated in the vasculature. However, recent work has shown that erythrocyte sequestration of hemoglobin, combined with flow, decreases oxyHb reaction with ‘NO and thus renders it less effective at antagonizing ‘NO bioactivity in the vessel lumen (1, 2). Also, the biological half-life of ‘NO, when determined under oxyHb-free conditions (0.1–3 s), is far shorter than expected rates of ‘NO autooxidation (3, 4). Both of these observations indicate that cell-dependent catalytic scavenging reactions will play a role in regulating ‘NO signaling.

Under pathological conditions of vascular dysfunction, accelerated ‘NO loss is often observed (5–7). In hypertensive states, a role for superoxide (O2⁻) reacting with ‘NO to form peroxynitrite (ONOO⁻) accounts for removal of a proportion of ‘NO. However, this is by no means the only mechanism for ‘NO removal because it is incompletely restored by O2⁻ scavengers (7). Nitric oxide consumption by bacterial flavohemoglobins forms NO2 via reaction with the oxy form (8–10) and is a proposed defense against “nitrosative stress.” Recently, rabbit and human 15-lipoxygenases were also found to catalytically consume ‘NO, through reaction with an enzyme-bound lipid peroxyl radical intermediate (E·−LOO) (11), indicating that mammalian cells also possess catalytic mechanisms for ‘NO removal.

In this report, a second mammalian enzyme, prostaglandin H synthase-1 (PGHS-1) is shown to also catalyze ‘NO consumption in both purified enzyme preparations and intact platelets. In platelets, the reaction of PGHS-1 with ‘NO led to inhibition of soluble guanylate cyclase, causing platelets to lose responsiveness to the antiaggregatory effects of ‘NO. Because platelet-derived ‘NO serves a central role in preventing aggregation following activation of soluble guanylate cyclase, these observations indicate that, in addition to the generation of eicosanoids, catalytic consumption of ‘NO by PGHS-1 can also contribute to its proaggregatory activity.

EXPERIMENTAL PROCEDURES

Materials—15(S)Hydroperoxyeicosatetraenoic acid (15(S)HPETE), prostaglandin H2 (PGH2), and U46619 were obtained from Cayman Chemical (Ann Arbor, MI). Arachidonic acid was from Sigma. 15(S)HPETE and PGH2 were stored at −80 °C in the dark under N2. Arachidonic acid and U46619 were stored at −20 °C in the dark. Before use, the sodium salts of arachidonic or 15(S)HPETE were prepared by dilution with 10% methanol, 0.01 M NaOH in water. U46619 and PGH2 were used as ethanolic solutions. All fatty acids were prepared from stocks on the day of the experiment, stored on ice, and discarded after use. Unless otherwise stated, all other chemicals were from Sigma.

PGHS-1 Assays—Apo-PGHS-1 was purified from ram seminal vesicles and stored at 3.76 mg·ml⁻¹ in 80 mM Tris, pH 7.8, at −80 °C (12, 13). For heme reconstitution, apo-enzyme was incubated with hematin (1, 2). Also, the biological half-life of ‘NO, when determined under oxyHb-free conditions (0.1–3 s), is far shorter than expected rates of ‘NO autooxidation (3, 4). Both of these observations indicate that cell-dependent catalytic scavenging reactions will play a role in regulating ‘NO signaling.

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¶ The abbreviations used are: oxyHb, oxyhemoglobin; PGHS, prostaglandin H synthase; HPETE, hydroperoxyeicosatetraenoic acid; L-NAME, N-nitro-L-arginine methyl ester; IBMX, 3-isobutyl-1-methylxanthine; PGH₂, prostaglandin H₂; PRP, platelet-rich plasma; GSNO, S-nitrosoglutathione; PGG₂, prostaglandin G₂.
Nitric Oxide Consumption by Prostaglandin H Synthase-1

TABLE I
Rates of nitric oxide uptake by purified PGHS-1

| Sample | Rate $k_{obs}$ | NO uptake constant $k_{obs} \cdot \text{min}^{-1}$ | NO concentration $\mu M$ |
|--------|---------------|---------------------------------|--------------------------|
| Background* | 1.96 ± 0.3 | 8.6 ± 1.6 $\times 10^{-3}$ | 0.998 |
| + PGHS-1 ^a | 1.96 ± 0.2 | 8.6 ± 1.6 $\times 10^{-3}$ | 0.995 |
| + PGHS-1, phenol ^a | 2.0 ± 0.1 | 9.0 ± 0.5 $\times 10^{-3}$ | 0.994 |
| + arachidonate | 7.13 ± 0.1 | (126 μM · min ^−1 · μM ^−1 PGHS-1) | NA |
| + apoPGHS-1, H_2O_2 ^a | 1.71 ± 0.4 | 7.5 ± 1.8 $\times 10^{-3}$ | 0.991 |
| + hematin, H_2O_2 ^a | 2.12 ± 0.2 | 9.5 ± 0.7 $\times 10^{-3}$ | 0.994 |
| + PGHS-1, H_2O_2, phenol | 29.4 ± 4.8 (517 μM · min ^−1 · μM ^−1 PGHS-1) | NA |
| + PGHS-1, 15/S/HPETE | 14 ± 1.8 (264 μM · min ^−1 · μM ^−1 PGHS-1) | NA |
| + apoPGHS-1, 15/S/HPETE ^a | 2.0 ± 0.1 | 8.9 ± 0.5 $\times 10^{-3}$ | 0.997 |
| + hematin, 15/S/HPETE | 3.8 ± 0.2 | 1.7 ± 0.1 $\times 10^{-3}$ | 0.997 |
| + PGHS-1, 15/S/HPETE, phenol | 16.7 ± 1.38 (294 μM · min ^−1 · μM ^−1 PGHS-1) | NA |

* For these samples, rates of NO loss at 3.8 μM were determined using the calculated first order rate constant ($k_{obs}$) for each sample. For all others, initial linear rates of NO loss on addition of PGHS-1 were determined ($n = 3$, means ± S.D.).

Results

Characterization of NO Loss in Reaction Systems—Nitric oxide decay in aerobic phosphate buffer followed first order kinetics with a rate constant (k_{obs}) of 8.6 ± 1.6 $\times 10^{-3}$ s^{-1}. Although aerobic oxidation of NO is second order overall (17), at the low NO concentrations used in this study alternative first order reactions predominate that include gas phase diffu-
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Nitric oxide (3.8 μM) was added to 0.5 ml of Tyrode’s buffer-containing platelets, 1 mM CaCl₂, 500 μM l-NAME, in the chamber of the NO electrode, at 37 °C with stirring. A, peak i, control, no platelets. Peak ii, Arachidonate (60 μM) was added to 5 × 10⁸ platelets as indicated by the arrow. Peak iii, arachidonate (60 μM) was added to platelets preincubated with 20 μM indomethacin for 10 min before addition of NO. Peak iv, arachidonate (60 μM) and PGH₂ (30 μM) were added together to indomethacin-pretreated platelets, as indicated. b, peak i, A23187 (300 nM) was added to 8 × 10⁸ platelets as indicated. Peak ii, platelets alone. Peak iii, A23187 (300 nM) was added to platelets preincubated with indomethacin as in c. Results of a representative experiment are shown, repeated at least three times, with different donors.

ionophore, A23187 (300 nM) (Fig. 1b). Unlike arachidonate, a lag period of 15–20 s was observed before a transient (20–30 s) rate of NO consumption was initiated. A23187-dependent NO consumption was partially inhibited by indomethacin, indicating that PGHS-1-dependent NO uptake was partially involved (Fig. 16).

Removal of NO by PGHS-1 Prevents Activation of Platelet Soluble Guanylate Cyclase—To elucidate the impact of NO consumption by PGHS-1 during platelet aggregation, platelet cGMP was determined following addition of exogenous NO (500 nM) and activation of platelets by arachidonate. Significant suppression of NO-stimulated soluble guanylate cyclase activity occurred following arachidonate activation of platelets and upon addition of oxyHb to scavenge NO (Fig. 2). The thromboxane A₂ agonist U46619, which activates platelet aggregation downstream of PGHS-1 without causing NO uptake (not shown), did not suppress stimulation of platelet cGMP generation (Fig. 2). These data indicate that PGHS-1-mediated NO consumption inhibits NO activation of soluble guanylate cyclase.

Platelet Responses to NO Are Greater with PGHS-1-independent Stimuli—To determine whether catalytic NO consumption influences platelet function, the sensitivity of platelets to NO-mediated inhibition of aggregation was evaluated following activation with arachidonate and the thromboxane A₂ mimetic, U46619, that does not suppress NO-dependent cGMP generation (Fig. 2). Both agonists trigger platelet aggregation via thromboxane receptor activation, the phosphorylation of which is partially responsible for inhibition of aggregation by NO (21). GSNO was utilized to provide a continuous source of NO, and l-NAME was added to prevent platelet NO generation. The requirement for NO in the platelet inhibitory effects of GSNO was indicated by full restoration of aggregation upon inclusion of 3 μM oxyHb (not shown). Concentrations of GSNO (0.5–2.0 μM) that had no effect on arachidonate-induced platelet aggregation fully inhibited aggregation induced by U46619 (Fig. 3). For partial inhibition of U46619-induced aggregation, only 1–20 nM GSNO was required, whereas up to 50 μM GSNO did not significantly impact arachidonate-induced aggregation (not shown). These data implicate PGHS-1-dependent NO consumption in the regulation of platelet responses to NO.
Nitric Oxide Consumption by Prostaglandin H Synthase-1

Nitric Oxide Is Consumed during Thrombin-induced Platelet Aggregation—For experiments utilizing thrombin, PRP was utilized since it is a more physiological platelet preparation (e.g. containing plasma-derived constituents such as albumin and lipoproteins). Nitric oxide or cGMP inhibits thrombin receptor signaling, including activation of platelet arachidonate release (22–24). To ensure that NO did not block arachidonate release, the order of agonist addition was reversed, with thrombin added to PRP 10 s prior to NO, and the peak of detectable NO then determined (Fig. 4B). When NO was added to PRP in the absence of agonists, the initial concentration of detectable NO was consistently lower than when NO was added to phosphate-buffered saline (a decrease of 1.1 ± 0.6 μM, n = 3 different PRP preparations, not shown). This may result from reaction of NO with contaminating oxyHb or the possible formation of S-nitrosothiols upon addition of NO to plasma (25). However, following NO addition to 0.04 unit/ml thrombin-activated PRP, a further and significant decrease in peak NO concentration was observed (representing a decrease of 0.8 ± 0.17 μM, n = 3 different donors; Fig. 4, a and b). This response was fully inhibited by indomethacin, indicating a requirement for PGHS-1 activity, and suppressed generation of cGMP by platelet soluble guanylate cyclase (Fig. 4, a and c). These data indicate that thrombin-stimulated PGHS-1 attenuates the antiaggregatory effects of NO in platelets.

Following platelet activation by collagen (4 μg/ml), indomethacin-insensitive but superoxide dismutase-inhibitable NO consumption was observed (not shown). This was expected because collagen stimulates platelet superoxide (O2-) generation through an uncharacterized pathway, and O2- reacts with NO at almost diffusion limited rates (26–28). Finally, NO consumption was not stimulated in PRP by ADP (5 μM) (not shown), possibly because of ADP being relatively less potent than thrombin (29, 30).

Hydroperoxides Stimulate Nitric Oxide Consumption by Purified Ovine Prostaglandin H Synthase—To determine the mechanism(s) by which platelet PGHS-1 could consume NO, purified PGHS-1 was utilized. In the absence of substrate, heme-reconstituted holoenzyme did not consume NO (Fig. 5A). However, either H2O2 or 15(S)HPETE stimulated PGHS-1 NO consumption dose-dependently (126 μM/min^−1 μM^−1 and 264 μM/min^−1 μM^−1 PGHS-1 using 400 μM H2O2 or 12 μM HPETE, respectively (Fig. 5, Table 1; and data not shown). 15(S)HPETE was the more potent co-substrate, because it is more efficiently reduced by the peroxidase activity of PGHS-1, having a K_m(app) of 3.27 ± 0.35 μM (Fig. 6A). Hydroperoxide-stimulated NO consumption by PGHS-1 required heme reconstitution (Fig. 5B) and was not inhibited by indomethacin. These data indicate that NO is consumed by acting as a reducing co-substrate for PGHS-1 peroxidase activity. The reducing substrate phenol did not stimulate PGHS-1-dependent NO consumption (not shown), excluding a reaction of NO with the ferric heme. However, phenol stimulated rates of both H2O2 and 15(S)HPETE-dependent NO consumption by PGHS-1, most likely through reaction of NO with phenoxyl radicals generated via one-electron oxidation of phenol by PGHS-1 compounds 1 and 2 (Fig. 5B and data not shown).

To further probe the mechanism of PGHS-1-dependent NO consumption, the fate of added 15(S)HPETE was examined. Following incubation with PGHS-1 and NO, 92% of the hydroperoxide substituent of 15(S)HPETE became undetectable, with retention of the characteristic conjugated diene spectrum (Fig. 6, b and c). The stoichiometry of NO consumed per mol 15(S)HPETE added was 2.14 ± 0.2 (r = 0.98) (Fig. 6D), consistent with NO acting as a reducing substrate for PGHS-1 reduction of LOOH to LOH (Scheme 1).

**DISCUSSION**

This study shows that PGHS-1 consumes NO via peroxidase-dependent mechanisms and that NO consumption by platelet
PGHS-1 attenuates the antiaggregatory actions of NO. This controlled catalytic mechanism for NO consumption and the consequent inhibition of NO signaling also reveals a concerted proaggregatory function of PGHS-1, the generation of eicosanoid products, and the catalytic consumption of NO.

Prostaglandin H synthase is a heme enzyme that catalyzes the initial steps of arachidonate oxidation required for eicosanoid synthesis. PGHS exhibits two distinct activities, a cyclooxygenase activity utilizing a tyrosyl radical intermediate to convert arachidonate to PGG2 and a heme-dependent peroxidase activity utilizing a tyrosyl radical intermediate to form PGHS complex. NO can terminate the catalytic tyrosyl radical,NO can interact with purified PGHS in multiple ways. NO concentrations do not appear to play a role under biological conditions, because it is effectively suppressed by arachidonate.

Nitric oxide interacts with purified PGHS in multiple ways. First, reaction of NO with the resting ferric heme to yield a nitrosyl complex occurs with equilibrium dissociation constant (Kd) of 0.92 mM (36). Because NO concentrations do not approach mM levels in vivo, this complex is not expected biologically. Second, NO can terminate the catalytic tyrosyl radical, forming 5-nitroso tyrosine, which rearranges to form 5-nitrotyrosine (37, 38). Although this reaction has allowed identification of the catalytic tyrosine residue as Tyr385, it does not appear to play a role under biological conditions, because it is effectively suppressed by arachidonate (39). Finally, NO can act as a reducing peroxidase substrate for PGHS-1, promoting reduction of 5-phenyl-4-pentenyl-hydroperoxide (40). Although reactions do take place (31–34). For example, oxidation of the heme by peroxides (32) HPETE. Results of a representative experiment, repeated at least three times are shown.

NO consumption by PGHS-1. a, Km (app) was determined by measuring initial rates of NO consumption by 56 nM PGHS-1 at varying 15(S)/HPETE concentrations. Michaelis-Menten parameters were calculated using Enzfitter (Elsevier Biosoft). Rates of NO consumption are plotted as v versus [v][f]. b, hydroperoxides were determined by leukemomyeloblast blue oxidation in samples generated as described under “Experimental Procedures.” Peak a, difference spectrum of 7.2 μM HPETE minus buffer. Peak b, difference spectrum of 7.2 μM HPETE and 56 nM PGHS-1 minus 56 nM PGHS-1 alone. Peak c, difference spectrum of 7.2 μM HPETE, 56 nM PGHS-1, and 19 μM NO minus 56 nM PGHS-1 and 19 μM NO. d, PGHS-1 (56 nM) was added to 0.5 ml of 100 mM phosphate buffer, pH 7.4, containing HPETE (0–1 μM) and NO (3.8 μM) at 37°C, with stirring. Amount of NO consumed was measured electrochemically by drawing tangents, and plotted against HPETE concentration (n = 3, means ± S.D.).

SCHEME 1. Mechanism of peroxidase-catalyzed nitric oxide consumption by PGHS-1.
and phosphorylation of the thromboxane receptor (21–24). Therefore, to explore the influence of thrombin on PGHS-1-dependent 'NO uptake, thrombin was added to platelets immediately before 'NO. In vivo, thrombin activation of platelets and thromboxane synthesis occurs and is elevated in vascular diseases including sickle cell anemia and atherosclerosis. Because 'NO is a central inhibitor of platelet-endothelial interactions in vivo, both the accelerated generation of thromboxane and exposure of platelets to 'NO will occur together in the vasculature.

Generation of 'NO by platelets in response to pro-aggregatory agonists acts as a negative feedback mechanism because aggregation is inhibited by 'NO (43–45). Platelet activation stimulates endogenous 'NO generation rates of between 0.004 and 1.35 nmol·min⁻¹·10⁶ platelets⁻¹ (43, 44, 46). Herein, platelet 'NO consumption of 0.1–0.4 nmol·min⁻¹·10⁶ platelets⁻¹ or 0.8 ± 0.17 µM by thrombin-activated PRP indicates that platelet 'NO removal will significantly impair 'NO-dependent signaling during aggregation. In support of this precept, activation of platelets by thrombin or arachidonate was found to significantly (i) suppress 'NO-dependent platelet cGMP generation and (ii) decrease the sensitivity of platelets to the antiaggregatory effects of 'NO.

In summary, PGHS-1 consumes 'NO via utilization as a reducing peroxidase substrate. Also, PGHS-1-dependent consumption of 'NO during platelet aggregation inhibits cGMP generation and decreases platelet sensitivity to the antiaggregatory effects of 'NO. The activation of PGHS-1 and subsequent generation of proaggregatory thromboxane A₂ plays a central role in platelet aggregation. Therefore, PGHS-1 consumption of 'NO is important because it (i) represents a novel proaggregatory function for PGHS-1 by serving as a regulatable biological sink for 'NO and (ii) demonstrates a controlled catalytic pathway for 'NO consumption by vascular cells.

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