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Thromboxane A₂ formation was monitored directly by measuring the rabbit aorta contractile activity generated in PRP by exogenous arachidonate or by thrombin. Thrombin was used to liberate endogenous fatty acid from platelet phospholipids. PGH₃ (0.1–2 µM), PGH₂ (0.1–2 µM), PGH₁ (up to 5 µM), and dibutyl cyclic AMP (up to 5 mM) did not alter the contractile activity formed by exogenous arachidonate (0.7 mM) in PRP (data not shown). However, very low levels of PGH₃ (0.3–0.5 µM) or PGH₂ (0.1 µM) inhibited arachidonate-induced PRP aggregation. In contrast, a 50% decrease in formation of contractile activity was induced by thrombin (10 units) in PRP preincubated with PGH₃ (0.4–0.7 µM), PGH₂ (0.3–0.6 µM), or dibutyl cyclic AMP (5 mM).

Both [¹⁴C]eicosapentaenoate and [¹⁴C]arachidonate were readily and similarly acylated into phospholipids when incubated with human platelets (Fig. 4 A and E). In addition, decacylation by thrombin or an ionophore (A-23187) of separately prelabeled platelets released comparable amounts of [¹⁴C]arachidonate or [¹⁴C]eicosapentaenoate, respectively (Fig. 4 B and F). Pretreatment of the arachidonate-labeled platelets with PGH₃ (Fig. 4C), PGH₂ (Fig. 4D), or PGH₁ (100 ng) markedly decreased the release of fatty acid and abolished the thromboxane formation. There was no increase in fatty acid release over basal levels when thrombin was added to labeled platelets treated with PGH₃ or PGH₂ (Fig. 4 C and D).

**Competition of Eicosapentaenoate with Arachidonate for Platelet Cyclooxygenase.** Unlabeled eicosapentaenoic acid and [¹⁴C]arachidonate were mixed in varying ratios and the reaction was initiated by the addition of washed platelets. The eicosapentaenoate effectively competed with arachidonate such that a 1:1 mixture of the fatty acids resulted in a 50% inhibition of formation of thromboxane B₂ and 12-hydroxyeicosatetraenoic and hydroxyhepaticatrienoic acids and block of arachidonic destruction (Fig. 5A). On the other hand, the eicosapentaenoate was a much poorer substrate for platelet cyclooxygenase, being converted only one-eighth as efficiently as arachidonate to thromboxane (Fig. 5B).

![Eicosapentaenoate metabolic pathway](image)

**Correction.** In the article "Synthesis of prostacyclin and thromboxane by bovine hypothalamus" by Anthony S. Liotta, David Gildersleeve, Michael J. Brownstein, and Dorothy T. Krieger, which appeared in the March 1979 issue of Proc. Natl. Acad. Sci. USA (76, 1448–1452), the authors request that the following correction be noted. In the legend to Fig. 2, the two sentences on lines 9–12 should read "An aliquot of the pooled extract was first allowed to react with the ACTH immunoabsorbent and activity not retained was then allowed to react with the β-endorphin immunoabsorbent. Activity retained on this latter column was eluted and subjected to Sephadex G-50 gel filtration (curve I)."

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Thromboxane A2 formation was monitored directly by measuring the rabbit aorta contractile activity generated in PRP by exogenous arachidonate or by thrombin. Thrombin was used to liberate endogenous fatty acid from platelet phospholipids. PGH3 (0.1-2 μM), PGH2 (0.1-2 μM), PGH1 (up to 5 μM), and dibutyryl cyclic AMP (up to 5 mM) did not alter the contractile activity formed by exogenous arachidonate (0.7 mM) in PRP (data not shown). However, very low levels of PGH3 (0.3-0.5 μM) or PGH2 (0.1 μM) inhibited arachidonate-induced PRP aggregation. In contrast, a 50% decrease in formation of contractile activity was induced by thrombin (10 units) in PRP preincubated with PGH3 (0.4-0.7 μM), PGH2 (0.3-0.6 μM), or dibutyryl cyclic AMP (5 mM).

Both [14C]eicosapentaenoate and [14C]arachidonate were readily and similarly acylated into phospholipids when incubated with human platelets (Fig. 4 A and E). In addition, deacylation by thrombin or an ionophore (A-23187) of separately prelabeled platelets released comparable amounts of [14C]-arachidonate or [14C]eicosapentaenoate, respectively (Fig. 4 B and F). Pretreatment of the arachidonate-labeled platelets with PGH3 (Fig. 4C), PGH2 (Fig. 4D), or PGH1 (100 ng) markedly decreased the release of fatty acid and abolished the thromboxane formation. There was no increase in fatty acid release over basal levels when thrombin was added to labeled platelets treated with PGH3 or PGH2 (Fig. 4C and D).

Competition of Eicosapentaenoate with Arachidonate for Platelet Cyclooxygenase. Unlabeled eicosapentaenoic acid and [14C]arachidonate were mixed in varying ratios and the reaction was initiated by the addition of washed platelets. The eicosapentaenoate effectively competed with arachidonate such that a 1:1 mixture of the fatty acids resulted in a 50% inhibition of formation of thromboxane B2 and 12-hydroxyeicosatetraenoic and hydroxyheptadecatrienoic acids and block of arachidonic acid destruction (Fig. 5A). On the other hand, the eicosapentaenoate was a much poorer substrate for platelet cyclooxygenase, being converted only one-eighth as efficiently as arachidonate to thromboxane (Fig. 5B).

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Correction. In the article "Influence of major histocompatibility haplotype on autoimmune disease varies in different inbred families of chickens" by Larry D. Bacon and Noel R. Rose, which appeared in the March 1979 issue of Proc. Natl. Acad. Sci. USA (76, 1435–1437), there was a printer’s error in Table 1. In this table, the groups of chickens that do not differ significantly in their immunological responses are joined by continuous lines. In the OSC subsets, for birds 6–10 weeks of age, the B5B5 group should be joined with the B5B13 and B13B13 groups. That is, the OSC B5B5 juvenile birds do not differ from those of other B haplotypes in development of thyroid autoimmunity.

Correction. In the article "Transformation of DBA/2 mouse fetal liver cells infected in vitro by the anemic strain of Friend leukemia virus" by D. W. Golde, N. Biersch, C. Friend, D. Tsuei, and W. Marovitz, which appeared in the February 1979 issue of Proc. Natl. Acad. Sci. USA (76, 962–966), the authors request that ref. 6 be corrected to read:

Triene prostaglandins: Prostacyclin and thromboxane biosynthesis and unique biological properties

(5,8,11,14,17-eicosapentaenoic acid/endoperoxides)

PHILIP NEEDLEMAN*, AMIRAM RAZ*, MARK S. MINKES*, JAMES A. FERRENDelli*, AND HOWARD SPRECHER

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ABSTRACT Platelets enzymatically convert prostaglandin H3 (PGH3) into thromboxane A2. Both PGH3 and thromboxane A2 aggregate human platelet-rich plasma. In contrast, PGH2 and thromboxane A3 do not. PGH3 and thromboxane A3 increase platelet cyclic AMP in platelet-rich plasma and thereby: (i) inhibit aggregation by other agonists, (ii) block the ADP-induced release reaction, and (iii) suppress platelet phospholipase-A2 activity or events leading to its activation. PGH3 (Δ17-prostacyclin; synthesized from PGH3 by blood vessel enzyme) and PGF2 (prostacyclin) exert similar effects. Both compounds are potent coronary relaxants that also inhibit aggregation in human platelet-rich plasma and increase platelet adenylate cyclase activity. Radioactive eicosapentaenoate and arachidionate are readily and comparably acylated into platelet phospholipids. In addition, stimulation of prelabeled platelets with thrombin releases comparable amounts of eicosapentaenoate and arachidionate, respectively. Although eicosapentaenoic acid is a relatively poor substrate for platelet cyclooxygenase, it appears to have a high binding affinity and thereby inhibits arachidonic acid conversion by platelet cyclooxygenase and lipooxygenase. It is therefore possible that the triene prostaglandins are potential antithrombotic agents because their precursor fatty acids, as well as their transformation products, PGH3, thromboxane A3, and PGF2, are capable of interfering with aggregation of platelets in platelet-rich plasma.

We previously demonstrated (1) that the fatty acid 5,8,11,14,17-eicosapentaenoic acid (C20:5) was converted by sheep seminal vesicle cyclooxygenase into a labile contractile substance that was a mixture of prostaglandin (PG) endoperoxides PGG3 and PGH3 (1). The 3-series endoperoxides were then enzymatically converted by platelet microsomes into a potent labile vasoconstrictor that was presumed to be thromboxane A3 (1, 2). In addition, application of purified PGH2 (produced from arachidonic acid) or PGH3 to isolated spiral strips of bovine coronary artery caused a transient relaxation, whereas PGH1 (produced by 8,11,14-eicosatrienoic acid) contracted the coronary strip (3). The primary product generated by bovine coronary arteries or by isolated perfused rabbit hearts from [14C]arachidonic acid was 6-keto-PGF1α (4–6), the stable end product formed from prostacyclin (PG12) (7) whereas [14C]eicosatrienoic acid was only converted to F2α (4, 8). These results indicated that the Δ5 double bond of PG endoperoxides is required for prostacyclin synthesis. Thus, PGH2 is the precursor of PG12 and its stable aqueous end product 6-keto-PGF1α, and PGH3 which is an active coronary relaxant was presumably converted to PG13 and ultimately degraded to its presumed end product Δ17-6-keto-PGF1α. However, no direct chemical or biological proof of this latter pathway has been reported.

Comparative study of the actions of metabolites of arachidonate and eicosapentaenoate on platelets in platelet-rich plasma (PRP) produced unexpected results. Arachidonate, PGH3, and thromboxane A2 were potent aggregators of human platelets but, in sharp contrast, the eicosapentaenoic acid, PGH3, or thromboxane A3 did not cause platelet aggregation (1, 2). Recently, this latter observation was given potential physiological perspective by the finding that Eskimos who have a bleeding tendency have elevated eicosapentaenoate and depressed arachidonate levels in their blood lipid fraction (9). It was suggested that endogenous PG13 synthesis from eicosapentaenoate by vasculature contributed to the bleeding tendency (9). However, no direct evidence of PG3 synthesis was presented, such as isolation and chromatographic identification of products or abolition of the synthesis of the antithrombotic substance with a prostacyclin synthetase inhibitor such as 15-hydroperoxyarachidonic acid. In addition, there is no evidence to indicate if the Eskimos’ bleeding disorder is due to a coagulation defect or to a platelet defect.

In the current investigation we document, biologically and chemically, the synthesis of PG3 and its inactive metabolite Δ17-6-keto-PGF1α, and of thromboxane A3 and its metabolite thromboxane B3. Furthermore, we analyze the unique actions of the triene PGs on human PRP and demonstrate an intrinsic platelet mechanism whereby PGH3 or thromboxane A3 inhibits aggregation by pro-aggregatory molecules.

MATERIALS AND METHODS

Materials. 5,8,11,14,17-[1-14C]Eicosapentaenoic acid (20:5), 7.2 CI/mol, was prepared by total organic synthesis (10). [14C]PGH3 was enzymatically synthesized (7-min incubation) and purified as described (1, 11). 15-Hydroperoxyarachidonic acid, an in vitro prostacyclin synthetase inhibitor (12), was synthesized from soybean lipooxygenase (13). Bovine aorta microsomes (BAM) were used as the source of prostacyclin synthetase and were prepared from freshly dissected vessels as described (5). Aspirin-treated platelet microsomes (APM) were employed as the source of thromboxane synthetase and prepared as previously described (1).

Vascular Smooth Muscle Bioassay. The bovine coronary artery and rabbit thoracic aorta assay tissues were hung in a vertical superfusion cascade and continuously bathed with Krebs–Henseleit solution (95% O2/5% CO2) at 10 ml/min as described (14–16).

Platelet Aggregation. Citrated human PRP or washed platelets were prepared as described (17).

Prostacyclin and Thromboxane Generation. The endoperoxide (PGH2 or PGH3) in acetone was dried in a stream of N2 and resuspended in 25 μl of phosphate buffer (50 mM, pH 7.4). The publication costs of this article were defrayed in part by page charge payment. This article must therefore be hereby marked "advertisement" in accordance with 18 U. S. C. §1734 solely to indicate this fact.

Abbreviations: PG, prostaglandin; PRP, platelet-rich plasma; BAM, bovine aorta microsomes; APM, aspirin-treated platelet microsomes.
7.4). Twenty microliters (80 µg of protein) of BAM was added to the endoperoxides and incubated for 1 min at room temperature. Twenty-five microliters (300 µg of protein) of APM was added to endoperoxide dissolved in phosphate buffer and incubated at 0°C for 2 min. The thromboxane synthetase inhibitor imidazole (18) was preincubated (5 mM) with the APM (or intact platelets) for 5 min.

Platelet Radiochemical Experiments. The 14C-labeled endoperoxide ([14C]PGH2 at 100,000 cpm or [14C]PGH3 at 60,000 cpm) was incubated with washed platelets (0.4 ml) at 37°C for 15 min, acidified to pH 3.5 with 2 M formic acid, and extracted twice with 2 vol of ethyl acetate. The extract was dried and applied together with unlabeled PG standards (kindly supplied by The Upjohn Company) to silica gel plates. The solvent system was benzene/dioxane/acetic acid, 60:30:3 (vol/vol).

[14C]Prostacyclin Generation. The 14C-labeled endoperoxides were dissolved in 25 µl of phosphate buffer and incubated with 25 µl of BAM at 37°C for 5 min. Acidification and extraction were carried out as described above. The solvent system (system A-9) was the organic phase from ethyl acetate/acetic acid/2,2,4-trimethylpentane/water, 110:20:50:10 (vol/vol).

Platelet Phospholipid Labeling Technique. Human blood was withdrawn into a syringe containing 1/13th vol of 77 mM EDTA and centrifuged for 10 min at 120 X g; the supernate was centrifuged at 4000 rpm for 6 min. The platelets were resuspended in 0.67 vol of albumin phosphate (33 mM, pH 6.5) containing 1 mg of glucose, 6.6 mg of NaCl, and 5 mg of fatty acid-poor bovine serum albumin per ml. [14C]Arachidonic acid (5 µg, 1.6 × 106 cpm) was dissolved in 100 µl of Tris buffer (100 mM, pH 9.0) and added to the platelet suspension which was incubated for 30 min at 37°C. The labeled platelets were centrifuged at 4000 rpm for 5 min and resuspended in calcium-free Krebs-Henseleit medium (pH 7.4).

Platelet Cyclic Nucleotide and ADP. Platelet cyclic AMP levels (at 60 sec) were determined by radioimmunoasay as described (19). The concentration of ADP released from aggregated platelets was measured enzymatically as described (17).

RESULTS

Biological and Radiochemical Characterization of PG12 and Thromboxane A2. Application of endoperoxide PGH2 or PGH3 resulted in a modest coronary relaxation and an aorta contraction (Fig. 1; ref. 3). Both endoperoxides were readily converted by BAM to a powerful coronary relaxant with the concomitant loss of any intact endoperoxide as evidenced by the loss of the aorta constricter. The enzymatically generated labile coronary relaxant is presumably PG12 because its synthesis is blocked by the prostacyclin synthetase inhibitor 15-hydroperoxyarachidonic acid. PGH1, which lacks the δ5 double bond necessary for the prostacyclin ring structure, is not converted by BAM to a coronary relaxant (3, 4, 8). Similarly, when the endoperoxides PGH2 and PGH3 were incubated with platelet microsomes, potent labile constrictor substances were generated. This enzymatic generation was blocked by imidazole, a thromboxane synthetase inhibitor.

Incubation of [14C]PGH3 with washed platelets generated a radioactive peak that comigrated with thromboxane B2 in the
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Fig. 3. Comparison of effects of diene and triene endoperoxide products (abbreviations as in Fig. 2; numbers are μg) on aggregation of human PRP.

benzene/dioxane/acetic acid solvent (Fig. 2 left). Pretreatment of the washed platelets with imidazole blocked the formation of a thromboxane-like peak and led to the appearance of PGE₂. The thromboxane B₂ or B₃ chromatography zone generated by the incubation of washed platelets with [¹⁴C]PGH₂ or [¹⁴C]-PGH₃, respectively, was extracted with chloroform/methanol, 2:1 (vol/vol) and each extract was applied to a AgNO₃-coated silica gel G plate; a clear separation of thromboxane B₂ from thromboxane B₃ was obtained (Fig. 2 bottom left). Radiochemical evidence of PGI₃ was obtained from the incubation of [¹⁴C]PGH₂ with BAM which led to the formation of a product that comigrated with 6-keto-PGF₁₋₀ (Fig. 2 right). 15-Hydroperoxyarachidonic acid blocked formation of the triene product (Fig. 2 middle right). 6-Keto-PGF₁₋₀ was separable from the Δ¹⁷-6-keto-PGF₁₋₀ (the presumed PGI₃ degradation product) on AgNO₃ plates (Fig. 2 bottom right).

The striking difference between the triene and diene products became apparent from studies of platelet function. Addition of arachidonate or PGH₂ (Fig. 3 top) or thromboxane A₂ (1) to human PRP resulted in a rapid irreversible aggregation and ADP-release reaction. In sharp contrast, neither PGH₃ nor thromboxane A₃ (i.e., PGH₃ plus APM) caused aggregation of PRP (Fig. 3 middle). Furthermore, pretreatment of PRP with either PGH₃ or thromboxane A₃ actually inhibited subsequent aggregation by other agonists including PGH₂ (Fig. 3 middle), thromboxane A₂ (Fig. 3 bottom), ADP, and collagen (not shown).

Effect of PGI₃ on Cyclic AMP Levels in PRP. Substances that increase platelet cyclic AMP levels inhibit platelet aggregation (20–23). Both PGH₃ (350 ng) and thromboxane A₃ increased cyclic AMP mean (±SEM) concentration (28 ± 4 and 22 ± 3 pmol of cyclic AMP per 400 μl of PRP, respectively); PGH₂ (200 ng) and thromboxane A₂ caused little or no change compared to control PRP (8 ± 5; n = 4). However, these data do not preclude the possibility that the increase in cyclic AMP induced by PGH₃ and thromboxane A₃ might be due to conversion to PGD₃ or PGE₃. PGI₃ (i.e., PGH₃ plus BAM increased cyclic AMP to 73 ± 6), PGI₂ (i.e., PGH₂ plus BAM increased cyclic AMP to 53 ± 1), and PGI₁ (300 ng increased cyclic AMP

Fig. 4. Radiochromatograms obtained from prelabeled human washed platelets (WP). (A and E) Lipid extract of platelets prelabeled with [¹⁴C]arachidonic acid ([¹⁴C]-[WP-AA*]) or with [¹⁴C]eicosapentaenoic acid ([¹⁴C]-[WP-EPA*]). The labeled lipids were extracted with 20 vol of chloroform/methanol, 2:1 (vol/vol), and separated with a solvent system of chloroform/methanol/NH₄OH, 65:35:5 (vol/vol). Abbreviations: NL, neutral lipids; FA, fatty acid; PE, phosphatidylethanolamine; PC, phosphatidylcholine. (B, C, and D) Arachidonate-prelabeled platelets stimulated with thrombin (1 unit) in control platelets (B), PGH₃ pretreated (450 ng) platelets (C), or PGI₂-pretreated (100 ng) platelets (D). (E) Eicosapentaenoic acid-prelabeled platelets treated with thrombin.
to 18 ± 3) all increase platelet cyclic AMP and inhibit platelet aggregation. PGH₂ has been demonstrated to increase cyclic AMP levels in PRP (11, 23).

Effect of PGH₃ on ADP Release Reaction and Thromboxane Synthesis. Preincubation of PGH₃ with PRP prevented aggregation and suppressed the ADP release induced by exogenous arachidonic acid. Addition of 50 µg of arachidonate to PRP caused complete aggregation and release of 8 µM ADP, and high concentrations of arachidonate caused no further ADP release (data not shown). As evidence that the platelets were not lysed by the arachidonate, subsequent lysis with Triton caused aggregation. In contrast, a 50% decrease in formation of contractile activity was induced by thrombin (10 units) in PRP preincubated with PGH₃ (0.4–0.7 µM), PGI₂ (0.3–0.6 µM), or dibutyryl cyclic AMP (5 mM).

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The release of a total of 20 µM ADP. Pretreatment of PRP with PGH₃ (100 ng) inhibited aggregation and ADP release. Thromboxane A₂ formation was monitored directly by measuring the rabbit aorta contractile activity generated in PRP by exogenous arachidonate or by thrombin. Thrombin was used to liberate endogenous fatty acid from platelet phospholipids. PGH₃ (0.1–2 µM), PGI₂ (0.1–2 µM), PGH₁ (up to 5 µM), and dibutyryl cyclic AMP (up to 5 mM) did not alter the contractile activity formed by exogenous arachidonate (0.7 mM) in PRP (data not shown). However, very low levels of PGH₃ (0.3–0.5 µM) or PGI₂ (0.1 µM) inhibited arachidonate-induced PRP

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**FIG. 5.** Eicosapentaenoate competition with arachidonate (AA) for platelet cyclooxygenase (A). Conversion of [¹⁴C]arachidonate (1 µg, 300,000 cpm) to eicosapentaenoic acid (EPA) was inhibited (B) converted only one-eighth as efficiently as arachidonate to thromboxane (Tx, thromboxane).

**FIG. 6.** Eicosapentaenoic acid metabolic pathway.
FIG. 7. PG metabolic pathways and sites of inhibition of the eicosapentaenoic acid (EPA) products on platelet aggregation. Tx, thromboxane; cAMP, cyclic AMP; AA, arachidonate; PL, phospholipid.

DISCUSSION

The synthetic pathway for the synthesis of the triene products is shown in Fig. 6. As a result of the additional Δ12-unsaturation (the only structural difference between PGH₂ and PGH₂) present in PGH₂ or thromboxane A₃, platelet adenylyl cyclase is stimulated and PRP aggregation and release are inhibited (Fig. 3). Conceivably, PGD₃ formation might also increase platelet cyclic AMP levels. On the other hand, PG₂ and PG₁₃ appear to exert similar effects both on vascular smooth muscle and on platelets.

PGH₃, PGH₂, and PG₁₃, which increase platelet cyclic AMP, do not appear to alter platelet cyclooxygenase activity as evidenced by their inability to depress thromboxane A₃ formation from exogenous arachidonate. On the other hand, at concentrations that block PRP aggregation, PGH₃, PG₁₃, and PG₁₂ also interfere with the liberation (presumably by phospholipase activation) of fatty acids from platelet phospholipids as evidenced by their blockade of thrombin-induced fatty acid release and formation of rabbit aorta contractile activity in PRP (Fig. 4 C and D). The finding that compounds that increase cyclic AMP in PRP also inhibit lipase activity agrees with results in washed platelets (17, 24). Such agents thus could be anticipated to interfere with thrombin-induced platelet aggregation. This effect differs from that of aspirin on platelets because aspirin does not block thrombin-induced aggregation (25).

Platelet aggregation might be suppressed by vascular synthesis of PG₁₃ (9). Dietary manipulations to increase the lipid content of eicosapentaenoic acid seems achievable because Greenland Eskimos have high levels of eicosapentaenoic acid and low levels of arachidonate in their serum lipids (9). However, the platelet lipids of the Eskimos have not been studied. We have in fact demonstrated that prostacyclin synthetase in isolated vascular segments will convert PGH₂ into PG₁₃. It has been hypothesized that the balance between the formation of thromboxane A₂ by the platelets and prostacyclin (PG₁₃) by the vascular walls regulates platelet aggregation and hemostatic plug formation in vivo (26). The present results indicate that vascular synthesis of PG₁₃ is not obligatory to suppress platelet aggregation. Thus, if platelet phospholipids were rich in eicosapentaenoic acid instead of arachidonate, then agonists such as collagen, thrombin, or ADP which stimulate platelet phospholipase A₂ would be expected to release eicosapentaenoic acid and to initiate intrinsic PG₁₃ and thromboxane A₃ synthesis. We have observed that the platelet cyclooxygenase is inefficient in converting eicosapentaenoic acid compared to arachidonate (Fig. 5B). However, the eicosapentaenoate effectively competes with arachidonate for platelet cyclooxygenase and lipoxygenase and thereby suppresses PGH₂ and thromboxane A₃ formation (Fig. 5A). In addition, any PG₁₃ and thromboxane A₃ formed would increase platelet cyclic AMP concentration and thereby endogenously inhibit aggregation by pro-aggregatory molecules and concomitantly inhibit platelet phospholipase activity. A schematic illustration of the sites for triene inhibition of platelet arachidonate metabolism and aggregation is shown in Fig. 7. Such mechanisms, possibly in concert with vascular PG₁₃ production, could be expected to decrease platelet aggregation.

Dietary manipulation of tissue fatty acids is possible. The acylation process seems to be nonselective because numerous unsaturated fatty acids can readily be incorporated into the phospholipid pool available for PG biosynthesis (27). In light of the demonstration that eicosapentaenoate can be incorporated into platelet phospholipids, a partial substitution of eicosapentaenoate for arachidonate in platelets might be useful in decreasing thrombotic tendencies and myocardial infarction.

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