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Arachidonic Acid Enhances the Tissue Factor Expression of Mononuclear Cells by the Cyclo-Oxygenase-1 Pathway: Beneficial Effect of n-3 Fatty Acids

Yves Cadroy, Dominique Dupouy, and Bernard Boneu

Monocytes express tissue factor (TF) upon stimulation by inflammatory agents. Dietary administration of fish oil rich in eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) results in an impairment of TF expression by monocytes. EPA and DHA are metabolized differently from arachidonic acid (AA), the major fatty acid present in cell membranes. We examined the effects of AA on the TF expression of isolated human PBMC, and we determined whether EPA and DHA modulated this phenomenon differently. Nonstimulated PBMC had a low TF-dependent procoagulant activity. When PBMC were incubated with increasing concentrations of AA, the TF-dependent procoagulant activity increased in a dose-dependent manner to 190% at 7.5 μM. Indomethacin, a cyclo-oxygenase inhibitor, totally abolished the stimulating effect of AA, whereas specific pharmacologic inhibitors of cyclo-oxygenase-2 or of 5-lipoxygenase had no inhibitory effect. A thromboxane (TX)A2/endoperoxides receptor antagonist and a TX synthase inhibitor blocked the potentiating effect of AA. Purified PGG2 and carbocyclic TXA2, a TXA2 agonist, enhanced the procoagulant activity of PBMC in a dose-dependent manner whereas, in contrast, PGE2 inhibited it. Finally, contrary to AA, EPA or DHA did not increase TXB2 production or TF expression by PBMC. The TF-dependent procoagulant activity of isolated PBMC was increased by AA through the production of cyclo-oxygenase-1 metabolites; the combined action of PGG2 and TXA2, which potentiated it, was greater than that of PGE2, which inhibited it. Dietary n-3 fatty acids exert part of their beneficial effect by modulating this procoagulant activity differently from AA.


A rachidonic acid (AA; 20:4, n-6) is a polyunsaturated fatty acid present in cell membranes that modulates diverse physiologic and pathologic responses. These effects are primarily mediated by its metabolic products, eicosanoids. Eicosanoids include notably the cyclo-oxygenase products, i.e., PG and TX, and the lipoxygenase products, i.e., leukotrienes and hydroxyeicosatetraenoic acids (HETEs). Their effects, which depend on the nature of compounds, principally concern inflammation and thromboregulation (1). Eicosapentaenoic acid (EPA; 20:5, n-3) and docosahexaenoic acid (DHA; 22:6, n-3) are other polyunsaturated fatty acids contained in fish oil. EPA is metabolized into eicosanoids that are different from the corresponding compounds derived from AA and are considered to develop reduced biologic activities (2–5). DHA is not metabolized by cyclo-oxygenase or lipoxygenase enzymes (6). Experimental (7, 8), epidemiologic, and interventional (9, 10) studies suggest that consumption of fish oil, which causes a progressive decrease in the AA content of tissue phospholipids and an increase in the tissue level of n-3 fatty acids, exerts beneficial effects on thrombosis and atherosclerosis. The molecular mechanisms by which dietary n-3 fatty acids exert their beneficial effects are complex and have not been totally clarified. Some of these effects have been attributed to the activity of n-3 fatty acids on monocytes (4, 8, 11–13).

Monocytes are centrally involved in numerous pathophysiologic processes, such as thrombosis, atherosclerosis, wound repair, and inflammation. These properties are partly related to their ability to express various procoagulant activities (14–17). The procoagulant activities of monocytes are mediated to a large extent by cell surface-associated tissue factor (TF). TF is the cellular receptor and cofactor for plasma factor VII(a), which initiates the coagulation protease cascade leading ultimately to the generation of thrombin and fibrin (18). Dietary administration of fish oil results in an impairment of TF expression by monocytes (8, 12, 13). The molecular mechanisms underlying TF activity reduction after n-3 fatty acids intake are unknown. However, since monocytes are important generators of eicosanoids and possess both cyclo-oxygenase and lipoxygenase enzymes, changes in the monocyte capacity to generate eicosanoids by these pathways have been suspected to influence monocyte TF activity. Thus, several recent studies have indicated that eicosanoids may modulate the procoagulant properties of monocytes. For example, prostacyclin analogues and PGE1 cause a decrease in cytokine-induced TF activity by monocytes (19, 20), whereas, conversely, platelet 12-HETE enhances PBMC procoagulant activity (21).

To clarify the mechanisms of the beneficial effect of dietary fish oil on the procoagulant activity of monocytes, we investigated in vitro the effects of AA, EPA, and DHA on TF expression by isolated PBMC. We show for the first time that AA, but not EPA or DHA, enhanced the TF-dependent procoagulant activity of PBMC. The roles of the cyclo-oxygenase and lipoxygenase pathways were also examined. We describe a novel role for the cyclo-oxygenase-1 pathway in modulating the TF expression of AA-stimulated PBMC that appeared to be balanced by the opposite effects of...
Materials and Methods

Cell isolation and cell cultures

PBMC were isolated using a modification of the method described by Balter et al. to efficiently deplete platelet from the cell preparation (22). Whole blood was obtained with a 19-gauge needle from healthy volunteers who had not taken aspirin or other nonsteroidal anti-inflammatory drugs in the 7 days preceding the donation. Blood was anticoagulated with trisodium citrate (0.129 M; Becton Dickinson, Meylan, France) and centrifuged at 280 × g for 15 min at 4°C. Platelet-rich plasma was removed. The sedimented cells were diluted to twice the original blood volume with PBS (pH 7.4; Gibco, Paisley, Scotland), layered on Hypaque PLUS (Pharmacia Biotech, Uppsala, Sweden), and centrifuged at 400 × g for 35 min at 4°C. The resulting PBMC were washed in 5 mL EDTA-PBS four to six times to remove remaining platelets. The resulting mononuclear fraction contained less than two platelets per leukocyte. Non-specific α-naphthyl-acetate esterase staining indicated that the mononuclear fraction contained 28.3 ± 6.4% (n = 4) monocytes. Cells (500 μL) were incubated at 2.5 × 10⁶ PBMC/mL in medium 199 (ATGC Biotechnologie, Noisy-le-Grand, France) containing 2 mM glutamine, 100 U/mL penicillin, and 100 μg/mL streptomycin in stoppered, sterile, pyrogen-free tubes.

Human endothelial cells were isolated from umbilical veins and cultured according to the method of Jaffe et al. (23). The culture medium was composed of RPMI 1640 and medium 199 (ATGC Biotechnologie, Noisy-Le-Grand, France) supplemented with 20% human pooled serum (Institut Jacques Boy, Reims, France). The cells were identified by their typical morphology. Cells were incubated for 4 h in medium 199 and carefully scraped with a rubber policeman just before measurement of their procoagulant activity.

Cell viability, as assessed by the measurement of lactate dehydrogenase release in the supernatant of cultured cells and by trypan blue exclusion, was >90%. All reagents used for cell isolation and culture were prepared with endotoxin-free water. The level of endotoxin contamination in the different reagents incubated with PBMC, as assessed by a sensitive chromogenic Limulus assay (Chromogenix, Molndal, Sweden), was very low (<0.001 ng/mL, final concentration). This level of endotoxin did not enhance the procoagulant activity of PBMC (data not shown).

Measurement of procoagulant activity

Procoagulant activity was measured on intact cells using a one-step plasma recalcification time assay performed on a coagulometer (KC4, Amelung, Lemgo, Germany). The PBMC were placed on ice for 10 to 20 min to remove any adherent monocytes. A 20-μL sample of PBMC or scrape-harvested endothelial cells was added to 90 μL of citrated normal human platelet-poor plasma. One hundred microliters of 25 mM CaCl₂ was added to initiate the reaction. Coagulation times were converted into procoagulant activity units (AU) using reference curves determined with a standard human brain TF preparation containing 10⁶ AU/mL (Thromborel S, Behring, Marburg, Germany); the logarithm of the procoagulant activity was related to the logarithm of the coagulation time. The procoagulant activity of mononuclear cells was characterized by incubating the cells with a mixture of two mouse anti-human TF mAbs (10 μg/mL; American Diagnostica, Greenwich, CT) for 30 min at 37°C.

Determination of TF, TXB₂, and PGE₂

TF Ag was measured on cell lysates by commercially available ELISA (Imubind Tissue Factor, American Diagnostica). Cell lysates were prepared by lysing PBMC in PBS containing 1% Triton X-100; 1 mM EDTA (Merck, Chelles, France), 16 mM octyl PG glucopyranoside (Boehringer Mannheim, Meylan, France), 10 μM peptakin A, 10 μM leupeptin, 0.1 mM PMSF (Sigma), and 100 kallkrein inhibitor units/mL aprotinin (Sanofi-Choay, Paris, France). The cell lysates were then frozen and thawed three times. They were stored at −80°C until assayed. TXB₂ and PGE₂ produced by cultured PBMC were measured in the supernatant by enzyme immunoassays (Cayman).

Statistical analysis

All results represent the mean ± 1 SEM of 4 to 10 separate experiments. Depending on the data, statistical analysis was performed using Student’s t test for paired variables or ANOVA followed by a Newman-Keuls test when p < 0.05. Differences were considered significant at p < 0.05.

Results

AA enhanced the procoagulant activity and TF synthesis of mononuclear cells

Nonstimulated PBMC had a very low procoagulant activity (138 ± 17 AU/10⁶ cells; n = 7). Considering that the procoagulant activity of the cell suspension was solely due to monocytes, which represented 28% of the PBMC suspension, the procoagulant activity expressed by monocytes (493 ± 61 AU/10⁶ monocytes) was comparable to that expressed by cultured resting endothelial cells (498 ± 110 AU/10⁶ endothelial cells; n = 9), indicating that monocytes were not significantly stimulated by the procedure of isolation. The procoagulant activity was TF dependent, since it was inhibited >90% by preincubating the cells with anti-TF mAbs. When PBMC cells were incubated with AA (5 μM) for 4 and 20 h, respectively, their procoagulant activity increased, but this increase was less marked with 4-h incubation (i.e., by 132% at 4 h vs 335% at 20 h; n = 1). Therefore, all additional experiments were performed with 20-h incubation. In these conditions, AA increased the procoagulant activity in a dose-dependent manner (Table I) to a mean of 190% at 7.5 μM (n = 10), which corresponds to a mean reduction in clotting times of 40 s (from 240 to 200 s). Higher concentrations resulted in cell lysis. Similarly, AA significantly enhanced the cell content of TF Ag (Table II). By comparison, LPS (100 ng/mL) increased the procoagulant activity of PBMC by 294% (406 ± 50 AU/10⁶ cells; n = 7).

The effect of AA was mediated by the cyclo-oxygenase-1 pathway

Preincubation of PBMC with indomethacin (10 μM), a cyclo-oxygenase-1 and -2 inhibitor, which blocked TXA₂ formation by 96 ± 1%, totally abolished the stimulating effect of AA, whereas specific pharmacologic inhibitors of cyclo-oxygenase-2 (NS398) or 5-lipoxygenase (L655,238) had no inhibitory effect (Table I). Importantly, the stimulating effect of AA was not due to a low contamination by endothocytes, since the procoagulant activity induced by LPS remained unchanged in the presence of indomethacin (563 ± 123 vs 570 ± 88 AU/10⁶ cells with and without indomethacin, respectively; n = 8). Therefore, these results indicate that AA enhanced the procoagulant activity of PBMC by the cyclo-oxygenase-1 pathway.

PGG₂ and CTXₐ₂ enhanced the procoagulant activity and TF synthesis of PBMC

The major metabolites of AA produced by the cyclo-oxygenase-1 pathway are represented by the endoperoxides PGG₂/PGE₂ and further metabolized into TXA₂, PGE₂, PGD₂, and PGFₐα. To determine those that are responsible for the enhancing effect of AA on the procoagulant activity of PBMC, we tested the effect of
purified PG (Table III). PGG2 and CTXα2, a TXA2 agonist, enhanced, in a dose-dependent manner, the procoagulant activity of PBMC and TF Ag (from 0.32 ± 0.12 to 1.15 ± 0.33 ng/106 cells at 2 μM PGG2; p < 0.05; n = 8). In contrast, PGE2 significantly decreased the procoagulant activity of the cells. TXB2, PGD2, and PGF2α had no significant effect.

To further test the hypothesis that the formation of endoperoxides and TXA2 was involved in the potentiating effect of AA on the procoagulant activity of PBMC, we studied the effect of furegrelate, a TX synthase inhibitor, which blocked TXA2 formation by 94 ± 1%, and that of SQ29,548, a TXA2-endoperoxides receptor antagonist. Both molecules inhibited the potentiating effect of AA on the procoagulant activity of PBMC (Table I). As expected, the procoagulant effect of CTXα2 was not inhibited by furegrelate (266 ± 51 vs 142 ± 30 AU/106 cells with and without CTXα2; 1 μM; p < 0.01; n = 4).

The potentiating effect of AA on the procoagulant activity of PBMC and the respective amounts of TXB2, the stable metabolite of TXA2, and PGE2 released by PBMC varied among the different blood donors from whom the cells were isolated. The effect of AA on the procoagulant activity of cells was not directly related to the amount of TXB2 or PGE2 released (p > 0.20), but was significantly and positively related to the ratio of TXB2/PGE2 formed by cells in presence of AA (r = 0.61; p < 0.001; Fig. 1). This correlation remained significant when the outlying data with the highest procoagulant activity (937% of the baseline procoagulant activity) were deleted (r = 0.44; p < 0.01). Therefore, the variability of response of blood donors to AA appeared to be related to the respective amount of endoperoxides/TXA2 and PGE2 produced by PBMC: there was a balance between these eicosanoids, which showed opposite effects on the procoagulant activity of PBMC.

To confirm that the procoagulant activity of PBMC was determined in part by a balance between TXA2 and PGE2, PBMC were incubated with PGE2 (0.5 μM) and increasing concentrations of CTXα2 (0 to 1 μM). As found previously (Table III), the addition of PGE2 to PBMC decreased their baseline procoagulant activity by 54% (Fig. 2). When the molar ratio CTXα2/PGE2 was increased from 0 to 2, the procoagulant activity of PBMC increased in a ratio-dependent manner. However, although the increase in procoagulant activity produced by the addition of CTXα2 to PGE2-treated cells was statistically significant (p < 0.01), the procoagulant activity of PGE2-treated cells remained significantly lower (p < 0.05) than that of cells incubated with CTXα2 but without PGE2 (p < 0.05).

**EPA and DHA did not enhance the procoagulant activity and TF synthesis of mononuclear cells**

The n-3 fatty acids EPA and DHA are metabolized differently from AA by cyclo-oxygenase and lipoxygenase enzymes. For example, when these fatty acids were incubated with PBMC, EPA, unlike AA, did not increase the basal production of TXB2, and DHA inhibited it (Table II). In these conditions, EPA and DHA did not enhance the procoagulant activity (Fig. 3) and TF Ag level (Table II) of PBMC. At 5 and 7.5 μM, the procoagulant activity was significantly lower with EPA and DHA (p = 0.01) than with AA. Therefore, these results confirm that the effect of AA was mostly mediated by the production of endoperoxides and TXA2.

**Discussion**

We have shown in the present study that the procoagulant activity of isolated PBMC was enhanced by AA. This increase in procoagulant activity was due to an increased generation of TF and not to an increased surface expression of procoagulant activity (Table II). The effect of AA was mediated through the production of cyclo-oxygenase-1 metabolites, especially endoperoxides and TXA2. These findings differ from those of a previous study in which AA enhanced the procoagulant activity of PBMC when they were

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**Table I. Effect of AA and of selective inhibitors of the cyclooxygenase and lipoxygenase pathways on the procoagulant activity of PBMC**

<table>
<thead>
<tr>
<th>AA (μM)</th>
<th>Control (AU/10⁶ cells, n = 10)</th>
<th>Indomethacin (AU/10⁶ cells, n = 9)</th>
<th>NS398 (AU/10⁶ cells, n = 8)</th>
<th>L655,238 (AU/10⁶ cells, n = 9)</th>
<th>Baicalein (AU/10⁶ cells, n = 10)</th>
<th>Furegrelate (AU/10⁶ cells, n = 10)</th>
<th>SQ29,548 (AU/10⁶ cells, n = 10)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>138 ± 17</td>
<td>193 ± 19**</td>
<td>236 ± 29**</td>
<td>261 ± 26**</td>
<td>116 ± 12</td>
<td>171 ± 21</td>
<td>182 ± 22</td>
</tr>
<tr>
<td>2</td>
<td>124 ± 22</td>
<td>128 ± 20</td>
<td>123 ± 22</td>
<td>145 ± 40</td>
<td>ND</td>
<td>191 ± 35</td>
<td>194 ± 36</td>
</tr>
<tr>
<td>5</td>
<td>128 ± 15</td>
<td>236 ± 31**</td>
<td>262 ± 44**</td>
<td>238 ± 55**</td>
<td>241 ± 33**</td>
<td>210 ± 34</td>
<td>194 ± 36</td>
</tr>
<tr>
<td>7.5</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>218 ± 22</td>
<td></td>
</tr>
</tbody>
</table>

* PBMC (2.5 × 10⁶ cells/mL) were incubated for 20 h with increasing concentrations of AA. Indomethacin (10 μM), NS398 (1 μM), L655,238 (1 μM), baicalein (10 μM), or furegrelate (10 μM), selective inhibitors of cyclooxygenase-2, 5-lipoxygenase, 12-lipoxygenase, and thromboxane synthase, respectively, and SQ29,548 (10 μM), a TXA2/endoperoxides receptor antagonist, were added to the cells before incubating PBMC with AA. For each inhibitor, statistical comparisons of the procoagulant activity of PBMC incubated in presence of AA vs that without AA are represented by asterisks, where * = p < 0.05, and ** = p < 0.01. Data are the mean ± 1 SEM of n experiments.

**Table II. Effect of AA, EPA, and DHA on TF Ag synthesis and TXB2 production by human mononuclear cells**

<table>
<thead>
<tr>
<th>AA</th>
<th>TFag (ng/10⁶ cells, n = 7)</th>
<th>TXB2 (pmol/10⁶ cells, n = 7)</th>
<th>TFag (ng/10⁶ cells, n = 5)</th>
<th>TXB2 (pmol/10⁶ cells, n = 7)</th>
<th>TFag (ng/10⁶ cells, n = 5)</th>
<th>TXB2 (pmol/10⁶ cells, n = 7)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 μM</td>
<td>0.4 ± 0.1</td>
<td>1.1 ± 0.1</td>
<td>0.4 ± 0.1</td>
<td>1.1 ± 0.1</td>
<td>0.4 ± 0.1</td>
<td>1.1 ± 0.1</td>
</tr>
<tr>
<td>5 μM</td>
<td>1.2 ± 0.4**</td>
<td>11.5 ± 1.2**</td>
<td>0.3 ± 0.1</td>
<td>1.1 ± 0.4</td>
<td>0.3 ± 0.1</td>
<td>0.2 ± 0.1**</td>
</tr>
</tbody>
</table>

* PBMC (2.5 × 10⁶ cells/mL) were incubated for 20 h with increasing concentrations of AA, EPA, or DHA. Statistical comparisons of PBMC incubated in presence of fatty acids vs PBMC without fatty acids are represented by asterisks, where ** = p < 0.01. TFag, tissue factor Ag. Data are the mean ± 1 SEM of n experiments.
stimulated by endotoxins and in presence of platelets. This result was related to the platelet lipoxygenase product, 12-HETE (21). The role of this platelet lipoxygenase product was negligible in our study, since the platelet/PBMC ratio was low (i.e., less than two platelets per leukocyte) and since baicalein, a pharmacologic inhibitor of platelet 12-lipoxygenase, did not inhibit the effect of AA (Table I). Our study was performed with nonstimulated PBMC. AA and other reagents were not contaminated with LPS; no detectable amount of endotoxin was found in the various molecules incubated with the cells, and the effect of AA was inhibited with indomethacin, contrary to that induced by LPS.

AA is metabolized by PBMC through different enzymatic pathways, notably cyclo-oxygenase-1, cyclo-oxygenase-2, and 5- and 12-lipoxygenases (22, 24–26). Leukotrienes, which are important modulators of the inflammatory response (27), were not involved in the enhancing effect of AA on the procoagulant activity of nonstimulated PBMC, since it was not affected by 5- and 12-lipoxygenase inhibitors (L655,238 and baicalein, respectively; Table I). In addition, previous studies have shown that leukotriene B₄ produced by the 5-lipoxygenase pathway, has no effect on the procoagulant activity of PBMC (21, 28). 12-HETE is a potent cofactor for TF generation by PBMC (21). However, in our working conditions, the amount of 12-HETE released may have been too low to have a role, since there were very few platelets, an important source of 12-HETE, and since monocytes produce only very low amounts of 12-HETE, especially in the absence of LPS (26).

The enhancing effect of AA observed in our study was mediated by cyclo-oxygenase-1. It was inhibited by indomethacin, a cyclo-oxygenase-1 and -2 inhibitor (29), but it remained unchanged with a selective inhibitor of cyclo-oxygenase-2 (NS398; Table I). The latter result is not surprising, since the cyclo-oxygenase-2 pathway is only functional when monocytes are exposed to inflammatory stimuli, which were absent in our study (24, 25). Interestingly, previous works and our own preliminary data indicate that pathways other than cyclo-oxygenase-1 are involved in the enhancing effect of AA on the procoagulant activity of PBMC when they are stimulated with LPS (21, 30).

Our experiments were performed with exogenous AA. However, we do consider the role of cyclo-oxygenase-1 pathway in AA-induced TF expression to be pathophysiologically relevant. Indeed, this polyunsaturated fatty acid was effective at concentrations as low as 5 µM. The plasma concentrations of polyunsaturated fatty acids have been reported to vary between 0.2 and 2 mM (31), and the percentage of AA in plasma free fatty acid can reach 9% (32). Interestingly, and in contrast to AA, endotoxin-stimulated TF expression of PBMC was not inhibited by inhibitors of the cyclo-oxygenase or lipoxygenase pathway. Thus, endogenous AA, present in the cell membrane, and/or the cyclo-oxygenase or lipoxygenase pathways did not appear to be involved in endotoxin-induced TF expression.

In the presence of AA, monocytes release endoperoxides (PGG₂ and PGH₂) through the cyclo-oxygenase-1 pathway that are further metabolized into two major metabolites, TXA₂ and PGE₂ (22, 24, 25). Purified PGG₂ and CTXA₂, a TXA₂ agonist, enhanced the TF

### Table III. Effect of purified prostaglandins on the procoagulant activity of mononuclear cells

<table>
<thead>
<tr>
<th>PG (µM)</th>
<th>0</th>
<th>0.5</th>
<th>1.0</th>
<th>2.0</th>
</tr>
</thead>
<tbody>
<tr>
<td>PGG₂ (AU/10⁶ cells, n = 8)</td>
<td>108 ± 10</td>
<td>ND</td>
<td>114 ± 32</td>
<td>146 ± 33**</td>
</tr>
<tr>
<td>CTXA₂ (AU/10⁶ cells, n = 4)</td>
<td>130 ± 33</td>
<td>174 ± 62</td>
<td>211 ± 28</td>
<td>272 ± 28*</td>
</tr>
<tr>
<td>TXB₂ (AU/10⁶ cells, n = 5)</td>
<td>122 ± 30</td>
<td>ND</td>
<td>120 ± 30*</td>
<td>116 ± 18</td>
</tr>
<tr>
<td>PGE₂ (AU/10⁶ cells, n = 9)</td>
<td>108 ± 10</td>
<td>80 ± 9</td>
<td>75 ± 4**</td>
<td>99 ± 8</td>
</tr>
<tr>
<td>PGE₂ (AU/10⁶ cells, n = 8)</td>
<td>154 ± 14</td>
<td>163 ± 30</td>
<td>160 ± 24</td>
<td>158 ± 20</td>
</tr>
<tr>
<td>PGE₂ (AU/10⁶ cells, n = 5)</td>
<td>149 ± 31</td>
<td>164 ± 40</td>
<td>139 ± 26</td>
<td>160 ± 46</td>
</tr>
</tbody>
</table>

* PGG₂ (2.5 × 10⁶ cells/mL) were incubated for 20 h with increasing concentrations of PGG₂, CTXA₂, TXB₂, PGE₂, PGD₂, and PGF₂α. Statistical comparisons of the procoagulant activity of mononuclear cells incubated in presence of PG vs that without PG are represented by asterisks, where * = p < 0.05 and ** = p < 0.01. Data are the mean ± 1 SEM of n experiments.
inducing a rise in the concentration of ionized calcium in the cell cytoplasm (1). Our study adds one more mechanism by which TXA₂ may be prothrombotic. Other mechanisms include its capacity to cause platelet aggregation and vasoconstriction, to augment monocyte and neutrophil adhesiveness (1, 35–38), and to promote diapedesis (3). Finally, our results also suggest that part of the antithrombotic effect of aspirin, which irreversibly inactivates cyclo-oxygenase and inhibits the production of endoperoxides/TXA₂, may be mediated by a diminution of the procoagulant activity of PBMC.

References


