Differential Regulation of Prostaglandin E\textsubscript{2} and Thromboxane A\textsubscript{2} Production in Human Monocytes: Implications for the Use of Cyclooxygenase Inhibitors

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Differential Regulation of Prostaglandin E$_2$ and Thromboxane A$_2$ Production in Human Monocytes: Implications for the Use of Cyclooxygenase Inhibitors$^1$

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There is an autocrine relationship between eicosanoid and cytokine synthesis, with the ratio of prostaglandin E$_2$ (PGE$_2$)/thromboxane A$_2$ (TXA$_2$) being one of the determinants of the level of cytokine synthesis. In monocytes, cyclooxygenase type 1 (COX-1) activity appears to favor TXA$_2$ production and COX-2 activity appears to favor PGE$_2$ production. This has led to speculation regarding possible linkage of COX isozymes with PGE and TXA synthase. We have studied the kinetics of PGE$_2$ and TXA$_2$ synthase under conditions that rely on COX-1 or -2 activity. With small amounts of endogenously generated prostaglandin H$_2$ (PGH$_2$), TXA$_2$ synthase was greater than PGE$_2$. With greater amounts of endogenously generated PGH$_2$, PGE$_2$ synthase was greater than TXA$_2$. Also, TXA synthase was saturated at lower substrate concentrations than PGE synthase. This pattern was observed irrespective of whether PGH$_2$ was produced by COX-1 or COX-2 or whether it was added directly. Furthermore, the inhibition of eicosanoid production by the action of nonsteroidal anti-inflammatory drugs or by the prevention of COX-2 induction with the p38 mitogen-activated protein kinase inhibitor SKF86002 was greater for PGE$_2$ than for TXA$_2$. It is proposed that different kinetics of PGE synthase and TXA synthase account for the patterns of production of these eicosanoids in monocytes under a variety of experimental conditions. These properties provide an alternative explanation to notional linkage or compartmentalization of COX-1 or -2 with the respective terminal synthases and that therapeutically induced changes in eicosanoid ratios toward predominance of TXA$_2$ may have unwanted effects in long-term anti-inflammatory and anti-arthritic therapy. The Journal of Immunology, 2000, 165: 1605–1611.

Prostaglandin E$_2$ (PGE$_2$)$^3$ and thromboxane A$_2$ (TXA$_2$) are members of a family of 20-carbon fatty acid derivatives, known collectively as eicosanoids. They are involved in normal physiology and in inflammatory responses (1, 2). Release of arachidonic acid (AA) from membrane phospholipids provides the primary substrate for eicosanoid synthesis (3, 4). AA is oxygenated by the cyclooxygenase (COX) enzyme, which synthesizes first the transient intermediate prostaglandin G$_2$ and then the unstable endoperoxide, prostaglandin H$_2$ (PGH$_2$) (5). PGH$_2$, as the substrate for PGE synthase and TXA synthase, is the common precursor for all of the two-series prostaglandins. Because PGE$_2$ and TXA$_2$ have opposing autocrine effects on cytokine production (6), it is important to understand how the ratio of these two mediators is regulated. Because PGE$_2$ and TXA$_2$ arise from the common intermediate PGH$_2$, their relative rates of production by a cell should depend on the relative efficiencies with which the respective terminal synthases engage PGH$_2$ and convert it to their eicosanoid products.

However, recent reports have suggested that the activities of the different COX isozymes, constitutive COX-1 and inducible COX-2, may be associated with different eicosanoids and products. For example, it was demonstrated in rat peritoneal cells that COX-2 activity favored PGE$_2$ or prostacyclin production, whereas COX-1 activity favored TXA$_2$ production (7, 8). To explain these findings, the authors suggested compartmentalization or functional linkage of COX isozymes with the different terminal synthases (7) or the induction of PGE synthase in conjunction with COX-2 (8, 9).

Confirming these observations, we observed in the present study that in the presence of COX-1 alone, TXA$_2$ was produced in excess of PGE$_2$, whereas after the induction of COX-2 the eicosanoid ratio was reversed. However, these conditions involve substantial differences in availability of PGH$_2$. Therefore, we examined to what extent differences in the kinetic properties of the terminal synthases may explain the differences in the ratios of PGE$_2$ and TXA$_2$, which had been attributed to the respective COX isozymes.

**Materials and Methods**

**Materials**

Materials were obtained from the following sources: AA and carboxyheptyl-imidazole (CI) (Sapphire Bioscience, Sydney, Australia); NS-398, rabbit PGE$_2$ anti-serum, and COX-1 and -2 Abs (Cayman Chemical, Ann Arbor, MI); PGH$_2$ (Calbiochem-Novabiochem, La Jolla, CA); TXA$_2$, thromboxane B$_2$ (TXB$_2$) antiserum prepared from a rabbit immunized with thromboxane conjugated to human thyroglobulin as used in previous studies (10); pyrogen-free Lymphoprep (Nycomed, Oslo, Norway); E-Toxase-Clean, LPS, zymosan, DTT, and glutathione (Sigma, St. Louis, MO); [5-(4-pyridyl)-6-(4-fluorophenyl)-2,3-dihydroimidazoo (2, 1-b) thiazolo] (SKF86002) (Calbiochem, San Diego, CA); 1α,25-dihydroxyvitamin D$_3$.
(11, 12). U937 cells were resuspended at 2 × 10⁶ cells/ml in RPMI 1640 supplemented with low-LPS 10% FCS and penicillin/gentamicin. Monocytes were stimulated with LPS (20 ng/ml final concentration) overnight in nonadherent teflon Minisorp tubes (Nunc, Copenhagen, Denmark) in a total incubation volume of 1 ml at 37°C with 5% CO₂. U937 cells were incubated overnight with 1 μM 1,25-dihydroxyvitamin D₃ (9.8 × 10⁻⁹ M) to promote monocytoid differentiation and then were stimulated with STZ (100 ng/ml final concentration) overnight or for the indicated times. After the incubation periods, cells were washed two times in RPMI and then resuspended in RPMI (no FCS) at 2 × 10⁶ cells/ml. AA was added and cells were incubated at 37°C with 5% CO₂ for 4 min, which was in the linear range of eicosanoid production (data not shown). AA was diluted and stored in ethanol at –20°C. PGH₂ was stored in ethanol at –70°C. Ethanol did not exceed 0.1% in experiments. The incubations were terminated by snap-freezing the cell suspension in ethanol/dry-ice bath. When pharmacologic agents were added, cells were preincubated with the agent for 5 min before the experiment, with the exception of SKF86002, which was incubated overnight during cell stimulation.

Disrupted cell preparations

Methods were adapted from those described previously (11, 12). U937 cells were resuspended at 10 × 10⁶ cells/ml of Tris-base buffer (0.1 M Tris, 1 mM glutathione, and 0.5 mM DTT) and then sonicated twice at 4 W for 1 min using a probe sonicator. The sonicate was centrifuged, and the cell pellets were discarded. PGH₂ was added and sonicate was incubated at 37°C with 5% CO₂ for 4 min. Western immunoblot

Cell pellets (5 × 10⁶) were resuspended in lysis buffer (HEPES-buffered HBSS (pH 7.4), 0.5% Triton X-100, 10 μg/ml PMSF, 10 μg/ml leupeptin, and 10 μg/ml aprotinin) and sample buffer (0.125 M Trizma base (pH 6.8), 20% glycerol, 4% SDS, and 0.1% 2-ME). The samples were then boiled for 5 min and loaded onto 12% acrylamide gel. Proteins were transferred for 4 h at 16 h for 300 mA current onto a Tris-blend membrane. The membranes were then soaked for 30 min at 25°C in TBS (25 mM Tris-HCl (pH 7.6), 0.2 M NaCl, and 0.15% Tween 20) containing 5% dried milk (weight to volume ratio) and then were exposed to anti-COX-1 or -COX-2. The membranes were then washed twice with TBS and incubated with HRP-conjugated donkey anti-rabbit Ab. Bound Abs were revealed with the enhanced chemiluminescence reagent following the manufacturer’s protocol (Amersham).

PGE₂ and TXA₂ measurements

Cell suspensions were stored at –20°C. Cell suspensions were centrifuged, and supernatants were used for eicosanoid measurements. TXA₂ has a half-life of ~30 s under physiological conditions and is converted to the stable metabolite TXB₂. TXE₂ and TXB₂ levels were determined by RIA.

Statistical analysis

Analyses were performed using a two-tailed Student’s t test. Significance as indicated on graphs represents p values <0.01.

Results

Effects of exogenous AA on eicosanoid production in resting and LPS-treated human monocytes

Freshly prepared human monocytes were prepared from peripheral blood by elutriation. In these cells, eicosanoid production increased in response to the addition of increasing concentrations of exogenous AA (Fig. 1a). At the lower end of the range of AA concentrations, TXA₂ was produced in excess of PGE₂. With a high concentration of AA, PGE₂ was produced in excess of TXA₂. The concentrations of AA at which the half-maximal rate of PGE₂ and TXA₂ production occurred were ~8 μM and 0.4 μM AA, respectively. The maximum rate of production for PGE₂ (18 ng/2 × 10⁶ cells/4 min) exceeded that of TXA₂ (10 ng/2 × 10⁶ cells/4 min).

COX-2 was induced in these cells by LPS treatment (Fig. 2). After cells were treated with LPS, the pattern of eicosanoid production in response to changing AA concentrations remained similar to that in resting cells (Fig. 1b). The concentrations of AA at which half-maximal rates of PGE₂ and TXA₂ production occurred were ~8 μM and 0.3 μM AA, respectively. The maximum rate of production of PGE₂ in response to the AA was greater in the LPS-treated cells (38 ng/2 × 10⁶ cells/4 min) than in resting cells (see above). In contrast, the maximum rate of TXA₂ production was similar in resting and LPS-treated cells (10 ng/2 × 10⁶ cells/4 min).
Effects of exogenous AA on eicosanoid production in resting U937 cells

Eicosanoid production in the human monocytic cell line U937 was similar to that seen in elutriated human monocytes (Fig. 3a). With concentrations up to ~3 μM AA, TXA₂ synthesis exceeded that of PGE₂. However, from 5 to 25 μM AA, there was no further change in the rate of TXA₂ synthesis, whereas PGE₂ levels increased substantially. Above 25 μM AA, there was no significant increase in either eicosanoid.

In response to exogenous AA, the maximum rates of production of PGE₂ and TXA₂ were 16 and 5 ng/2 × 10⁶ cells/4 min, respectively. The concentrations of AA at which the half-maximal rates of PGE₂ and TXA₂ production occurred were 11.5 μM and 0.8 μM AA, respectively.

Effects of exogenous AA on eicosanoid production in STZ-treated U937 cells

COX-2 was induced when U937 cells were treated with STZ (Fig. 4). Under these conditions, there was greater production of both PGE₂ and TXA₂ in response to exogenous AA compared with unstimulated cells (Fig. 3b). The maximum rates of production of PGE₂ and TXA₂ synthesis in STZ-treated cells were 29 and 9 ng/2 × 10⁶ cells/4 min, respectively, i.e., approximately double the values for resting cells. By contrast, the concentrations of AA-producing half-maximal rates of eicosanoid production were similar to those in resting cells, namely, 10.5 μM AA for PGE₂ and 0.7 μM AA for TXA₂.

FIGURE 2. Effect of LPS on COX-2 levels in nonadherent human monocytes. Fresh monocytes after 24 h treatment with LPS were examined for COX-2 levels by Western immunoblot.

FIGURE 3. PGE₂ and TXA₂ production in U937 cells. a. Resting cells, i.e., untreated except for the addition of AA; the incubation was terminated after 4 min. b. STZ-treated cells; after pretreatment with 1α,25-dihydroxvitamin D₃ for 24 h, cells were treated with STZ for a further 24 h, and then cells were washed and treated with AA for 4 min. The results shown are the mean ± SD from three separate experiments.

FIGURE 4. Western immunoblot for COX-1 and -2 in U937 cells. After pretreatment with 1α,25-dihydroxyvitamin D₃, cells were or were not treated with STZ for 24 h. Cells were prepared for immunoblot as described in Materials and Methods.

FIGURE 5. Effect of TXA synthase inhibition on PGE₂ production in U937 cells. a. Resting cells; cells were pretreated with the TXA synthase inhibitor CI for 5 min before the addition of AA; the incubation was terminated after 4 min. b. STZ-treated cells; after pretreatment with 1α,25-dihydroxyvitamin D₃ for 24 h, cells were treated with STZ for a further 24 h, and then cells were washed and treated with CI for 5 min and then with AA for 4 min. The results shown are the mean ± SD from three separate experiments.
Because the results with U937 cells were similar to those with freshly prepared elutriated human monocytes, the U937 cells were used for the remaining experiments.

**Effects of TXA synthase inhibition**

U937 cells were preincubated with the TXA synthase inhibitor CI for 5 min before the addition of increasing concentrations of exogenous AA. There was >85% inhibition of TXA 2 synthesis and an increase in PGE 2 synthesis at all concentrations of AA in resting (Fig. 5a) and STZ-treated (Fig. 5b) cells.

**Effect of PGH 2 on disrupted cells**

Exogenous PGH 2 was added in increasing concentrations to sonicated U937 cell preparations as described in Materials and Methods. At concentrations of PGH 2 of 10 μM or less, TXA 2 synthesis exceeded that of PGE 2 synthesis (Fig. 6). At higher concentrations, PGE 2 was the predominant eicosanoid produced. The Kms (Michaelis constant) for PGE and for TXA synthase were 17 and 1 μM PGH 2, respectively.

**Effects of aspirin**

Aspirin, an irreversible COX inhibitor, was used at two doses to reduce PGH 2 production incrementally. U937 cells were preincubated for 5 min with aspirin before the addition of AA. At all concentrations of AA, aspirin inhibited PGE 2 synthesis to a greater extent than TXA 2 synthesis (Fig. 7). There was a dose-dependent inhibition of PGE 2 synthesis by aspirin, and this was seen at essentially all concentrations of exogenous AA examined. By contrast, aspirin had no effect on TXA 2 synthesis at the lower dose and only a modest inhibitory effect at the higher dose of aspirin. Similar results were seen in STZ-treated cells in which COX-2 was induced (Fig. 7), except that no significant inhibition of TXA 2 production was seen even at the higher dose of aspirin.

**Effects of suppression of COX-2 induction**

The p38 mitogen-activated protein kinase inhibitor SKF86002 is an inhibitor of COX-2 induction (13). At all concentrations of exogenous AA, 10 and 100 nM SKF86002 inhibited PGE 2 synthesis, whereas TXA 2 synthesis was unaffected (Fig. 8).

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**FIGURE 6.** PGE 2 and TXA 2 production by sonicates of resting U937 cells in response to exogenous PGH 2. Cells were washed, sonicated, and incubated with exogenous PGH 2. Incubations were terminated after 4 min. The results shown are the mean ± SD from two separate experiments.

**FIGURE 7.** Effect of aspirin on PGE 2 and TXA 2 production in U937 cells. a and b, Resting cells; cells were washed and preincubated with aspirin for 5 min, after which exogenous AA was added. The incubations were terminated after 4 min. c and d, STZ-treated cells; after pretreatment with 1α,25-dihydroxyvitamin D 3 for 24 h, cells were treated with STZ for a further 24 h, and then cells were washed and treated with aspirin for 5 min and then with AA for 4 min. The results shown are the mean ± SD from three separate experiments.
Effects of TXA synthase and COX-2 inhibition on the time course of eicosanoid production by STZ-stimulated cells

To assess production of PGE$_2$ and TXA$_2$ at different stages of COX-2 induction, supernatants were assayed at several time points after STZ addition (Fig. 9). TXA$_2$ was detectable after 1 h and was seen in increasing amounts at subsequent times. By contrast, PGE$_2$ was not detectable until 4 h. Both SKF86002 (an inhibitor of COX-2 induction) and NS-398 (a selective COX-2 inhibitor) inhibited PGE$_2$ synthesis more completely than TXA$_2$.

Eicosanoid accumulation was also measured at intervals after cells were stimulated with STZ either in the presence or absence of the TXA synthase inhibitor CI (Fig. 10). In the absence of CI, the initial accumulation in TXA$_2$ exceeded that of PGE$_2$. In the presence of CI, TXA$_2$ production was minimal and was exceeded by PGE$_2$ throughout. The quantity of PGE$_2$ produced in the presence of CI was approximately equal to the aggregate amounts of PGE$_2$ and TXA$_2$ produced in the absence of CI.

Discussion

The synthesis of PGE$_2$ and TXA$_2$ occurs through a series of enzymatic steps. The early steps of AA release by phospholipase A$_2$ and production of PGH$_2$ by COX are common to both eicosanoids, and the activities of these initial enzymes are prime determinants of the rate of eicosanoid production (4, 14). However, we have shown that the differing kinetics for PGE synthase and TXA synthase enzymes create a situation in which the ratio of PGE$_2$/TXA$_2$ in response to cell stimulation and AA availability follows a more complex pattern. Furthermore, this ratio can be perturbed in important ways by anti-inflammatory agents.

The issue of proportionate production of PGE$_2$ and TXA$_2$ has been addressed only recently using rat peritoneal exudate cells. In these cells, both endogenous AA (liberated by A23187) and a single dose of exogenous AA led to synthesis of TXA$_2$ in excess over PGE$_2$. However, when the cells were treated with LPS or TNF-α to induce COX-2, there was an alteration in eicosanoid ratios to an excess of PGE$_2$ over TXA$_2$ production (7–9). To explain these results, it was suggested that COX-1 and COX-2 are functionally coupled to different terminal synthase enzymes (8, 9) or that the results were because of different intracellular distributions of COX-1 and COX-2 and different intracellular locations of the terminal synthases (7). This notion has been referred to previously as compartmentalization (15, 16). This explanation for the differential regulation of PGE$_2$ and TXA$_2$ remains speculative and does not take into account other possibilities arising from the enzyme kinetics of the terminal synthases.

Because both PGE synthase and TXA synthase can be expected to have distinctive kinetic properties and because these properties will influence the ratio of PGE$_2$ and TXA$_2$ produced under conditions of differing AA/PGH$_2$ availability, we undertook to determine their response to changing substrate concentrations in human monocytes. The patterns of eicosanoid synthesis in response to increasing AA concentrations in fresh human monocytes were similar to those in the human monocytic-cell line U937, which had been treated with 1α,25-dihydroxyvitamin D$_3$ to induce monocytoid maturation (17, 18). The major difference between fresh human monocytes and the U937 cells was the increase in maximum
PGH₂ to saturate PGE synthase. COX-1 and -2 become rate limiting before providing enough AA in the presence of both COX-1 and -2. These results suggest that saturated. This was seen in both resting and STZ-treated cells, i.e., COX inhibition was added along with STZ. At the indicated times, the cell supernatant mixture was removed and frozen for later measurement of cumulative eicosanoid production. The results shown are the mean ± SD from three separate experiments.

FIGURE 10. The effect of TXA synthase inhibition on cumulative PGE₂ and TXA₂ production in U937 cells. Cells were preincubated with 1α,25-dihydroxyvitamin D₃ for 24 h, after which the TXA synthase inhibitor CI was added along with STZ. At the indicated times, the cell supernatant mixture was removed and frozen for later measurement of cumulative eicosanoid production. The results shown are the mean ± SD from three separate experiments.

velocity for TXA synthase after cell stimulus seen in the latter. This is in accord with the effects of 1α,25-dihydroxyvitamin D₃, which is a known inducer of TXA synthase (19).

In resting U937 cells, we detected only COX-1, whereas in STZ-treated cells, COX-2 was also detected. In the presence of COX-1 or COX-2, there were three distinct ranges of exogenous AA based on the profile of the eicosanoids produced.

First, with the addition of <5 μM AA, TXA₂ was produced in greater amount than PGE₂, suggesting that TXA synthase has a higher rate constant than PGE synthase. Second, from 5 to 25 μM AA, there was an increase in PGE₂ synthesis, whereas TXA₂ synthesis was unchanged. The increasing amount of PGE₂ in this range of AA indicates that COX was not saturated with AA and that COX-1 and -2 were not rate limiting for PGE₂ production. However, the plateau in TXA₂ production suggests that the TXA synthase had become saturated. Third, with the addition of >25 μM AA, there was a plateau in PGE₂ synthesis, suggesting that either COX or PGE synthase had become saturated. Overall, these findings establish PGH₂ concentration and the kinetic properties of either COX or PGE synthase had become saturated. These results suggest that COX-1 and -2 become rate limiting before providing enough PGH₂ to saturate PGE synthase.

To determine whether the lack of increase for PGE₂ production in response to >25 μM exogenous AA was due to COX or PGE synthase saturation, experiments using the TXA synthase inhibitor CI (20) were performed. In the presence of a constant amount of AA, TXA synthase inhibition is expected to increase the availability of PGH₂ for PGE synthase (by preventing PGH₂ catalysis to TXA₂). If PGE synthase was saturated by >25 μM AA, there should be no further increase in PGE₂ production with CI present. However, we observed an increase in PGE₂ production at >25 μM AA in the presence of CI, indicating that PGE synthase was not saturated. This was seen in both resting and STZ-treated cells, i.e., in the presence of both COX-1 and -2. These results suggest that COX-1 and -2 become rate limiting before providing enough PGH₂ to saturate PGE synthase.

Although the interpretation of the results of experiments utilizing exogenous AA is limited in its application to that with endogenous AA, the results regarding relative eicosanoid production in both circumstances were similar. With cell stimulation, endogenous AA is mobilized from membrane phospholipids for the production of eicosanoids (21). The production of PGE₂ characteristic is detectable from 2 to 6 h after stimulation (9, 15, 22), the time at which COX-2 up-regulation is detectable (23). Importantly, we have shown that TXA₂ was produced significantly earlier than PGE₂. This has been observed in fresh, nonadherent human monocytes (G.E.C., unpublished data); adherent human monocytes (24); and murine macrophages (25) as well as in animal models of inflammation (26). As was the case with exogenous AA, this finding also supports the proposal that TXA synthase, compared with PGE synthase, has a greater affinity for PGH₂, whether the latter is synthesized from endogenous or exogenous AA. Additionally, we demonstrated that after STZ exposure, the time of onset of PGE₂ production from endogenous AA could be shortened from 4 h to 1 h by the addition of the TXA synthase inhibitor CI. Thus, the important factor involved in PGE₂ production from endogenous AA appears to be the availability of PGH₂ rather than presence of the COX-2 isozyme.

To examine more directly the influence of PGH₂, exogenous PGH₂ was used to compare the kinetic parameters of the terminal synthases. The Km and maximum velocity values for PGE synthase were greater than those for TXA synthase. This order was similar to the relativities of the apparent kinetic parameters for the terminal synthases estimated by the use of exogenous AA. The values are similar to those previously reported in disparate cell systems. (12, 27–29).

The observed kinetic differences in PGE synthase and TXA synthase predict differential effects on PGE₂ and TXA₂ synthesis by COX inhibition. Aspirin, an irreversible inhibitor of COX (30), was used to inhibit eicosanoid production in response to exogenous AA in resting and STZ-treated cells. Aspirin was chosen over other nonsteroidal anti-inflammatory drugs (NSAID) because increasing AA concentrations cannot reverse the COX inhibition. Because aspirin has a lower ID₅₀ for COX-1 than for COX-2 (31), higher concentrations were used to inhibit COX-2. It was observed that in both unstimulated cells (expressing COX-1 alone) or stimulated cells (expressing predominantly COX-2), PGE₂ production was much more sensitive to inhibition by aspirin than TXA₂. The differential inhibition of eicosanoid production by aspirin thus favors synthesis of TXA₂ relative to PGE₂ in the presence of COX-1 or COX-2.

The family of p38 mitogen-activated protein kinase inhibitors, of which SKF86020 is a prototypic member, inhibits mononuclear cell IL-1β and TNF-α production. Members of this class are currently under development for clinical applications. We have shown previously that SKF86020 inhibits COX-2 induction in elictruated human monocytes (13). Cell suspensions were incubated overnight with LPS in the presence of increasing concentrations of SKF86020 to inhibit COX-2 induction incrementally. For cells that were then washed and treated with exogenous AA, PGE₂ production was inhibited by SKF86020 in a dose-dependent manner, whereas TXA₂ synthesis was unaffected.

When the production of PGE₂ and TXA₂ was followed in STZ-treated cells in the presence of either SKF86020 or the selective COX-2 inhibitor NS-398, it was found that both PGE₂ and TXA₂ synthesis were inhibited but that the inhibition was greater for PGE₂. Thus, PGF₂ synthesis was shown to be more influenced by strategies that reduced availability of PGH₂ (derived from endogenous AA) than was TXA₂ synthesis.

In summary, an NSAID, a selective COX-2 inhibitor and an inhibitor of COX-2 induction, preferentially decreased PGE₂ compared with TXA₂ synthesis. This was the case whether PGH₂ was formed from exogenous or endogenous AA or whether it was synthesized by COX-1 or COX-2.
The clinical implications of these findings may be important, particularly with regard to use of NSAID and selective COX-2 inhibitors, because a shift in the PGE\textsubscript{2}/TXA\textsubscript{2} balance in favor of TXA\textsubscript{2} may increase synthesis of the inflammatory cytokines IL-1\textbeta and TNF-\alpha (6). Thus, the short-term effects of these agents on the pain and swelling of inflammation and arthritis may be achieved at the cost of an increased propensity to long-term tissue damage with which these cytokines have been associated.

With regard to the mechanisms of regulation of PGE\textsubscript{2} and TXA\textsubscript{2} production by monocytes, our data show that the extent of PGH\textsubscript{2} generation coupled with the respective kinetic properties of PGE and TXA synthase are important determinants of the ratio of PGE\textsubscript{2}/TXA\textsubscript{2} produced.

References


