Deficient Lipoxin Synthesis: A Novel Platelet Dysfunction in Myeloproliferative Disorders With Special Reference to Blastic Crisis of Chronic Myelogenous Leukemia

By Leif Stenke, Charlotte Edenius, Jan Samuelsson, and Jan Åke Lindgren

The capacity to convert exogenous leukotriene A\(_\text{\alpha}\) to lipoxins (LXs) was investigated in platelet suspensions from patients with myeloproliferative disorders (MPD) (n = 22) and healthy control subjects (n = 14). Platelets isolated from the controls produced mainly LXA\(_\text{\alpha}\), but also 6(S)-LXA\(_\text{\alpha}\) and the all-trans isomers of lipoxins A\(_\text{\alpha}\) and B\(_\text{\alpha}\) as determined by high-performance liquid chromatography and computerized UV spectroscopy. In comparison to control levels, the mean LX synthesis was significantly lower in platelets from the MPD patients (438.7 ± 62.8 and 157.4 ± 31.2 pmol LXA\(_\text{\alpha}\) per 10\(^6\) platelets, respectively; mean ± SEM; P = .0001). Platelets from six of the patients showed a particularly low capacity to produce LXs, resulting in LX levels below the detection limit or less than 7% of mean control levels. Notably, all these patients were in blastic crisis of chronic myelogenous leukemia (CML). This severely deficient LX production was paralleled by a dramatically attenuated conversion of arachidonic acid to 12-HETE (12-hydroxyeicosatetraenoic acid), while the formation of HHT (12-hydroxyheptadecatrienoic acid), a product formed via the prostaglandin endoperoxide synthase pathway, was normal. In addition, longitudinal studies of CML patients showed that blastic metamorphosis was associated with a markedly reduced capability to synthesize LXs, while this capacity improved after retransformation into a second chronic phase. The results reveal deficient LX synthesis as a novel platelet dysfunction in MPD, particularly in blastic crisis of CML in which an essentially abolished 12-lipoxygenase activity may be a general phenomenon.

MATERIALS AND METHODS

Clinical material. Blood samples were obtained from 13 patients with CML, six with polycythemia vera (PV), three with chronic myelogenous leukemia (CML), and 14 healthy volunteers. All patients were collected with the informed consent of involved individuals in accordance with the approval of the project from the Ethics Committee of Karolinska Institutet. The clinical and laboratory characteristics of the CML patients are shown in Table 1. Two of the patients in chronic phase ("B" and "D") were Philadelphia chromosome (Ph) negative, but both displayed low leukocyte alkaline phosphatase (LAP) scores and a typical morphologic blood and bone marrow picture compatible with the CML diagnosis. Patient "D" also presented with a moderate myelofibrosis. Clinical characteristics of CML patients in blastic crisis are described in Results. None of the patients with PV or ET received cytoreductive therapy or nonsteroidal anti-inflammatory drugs (NSAID) within 2 weeks before testing, except one ET patient regularly taking 500 mg aspirin twice weekly. All healthy volunteers were without medication.

Materials. Arachidonic acid was purchased from Nu-Check Prep Inc (Elysis, MN). Synthetic LTA\(_\text{\alpha}\), methyl ester was supplied by Salford Ultrafine Chemicals (Manchester, UK) and saponified with NaOH to give the free acid. Mesangial cells were prepared from rat kidneys as described previously.

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was from Biomol Research Laboratories (Plymouth Meeting, PA). The dihydroxy acid S(S),12(S)-DHETE was biosynthesized as 5-hydroxyeicosatetraenoic acid (HETE) and 12-HETE, as well as LTB, C, D, and E, were kind gifts of Dr T. Miyamoto (ONO Chemicals Ltd, Osaka, Japan). Biosynthetic 12-hydroxyheptadecatrienoic acid (HHT) was generously provided by Dr P. Westlund (Karolinska Institutet, Stockholm, Sweden). Synthetic 15-HETE was from Biomol Research Laboratories (Plymouth Meeting, PA). The dihydroxy acid 5(S),12(S)-DHETE was biosynthesized as described.16 LXA, and B, were purchased from Cayman Chemical Co (Ann Arbor, MI), while 6(S)-LXA, and all-trans isomers of LXA, and B, were kindly provided by Dr K.C. Nicolaou (University of Pennsylvania, Philadelphia). All solvents of high-performance liquid chromatography (HPLC) grade were from Rathburn Chemicals Ltd (Walkerburn, Scotland).

Preparation of cells. Peripheral blood samples were obtained through venepuncture and collected in tubes containing EDTA (77 mmol/L, 7.5% vol/vol). After initial centrifugation at 200g for 15 minutes, the platelet-rich plasma was collected and centrifuged at 650g for 20 minutes. The platelet-containing pellet was washed twice in Tris-buffered saline containing 6.2 mmol EDTA/L and resuspended in phosphate-buffered saline (PBS; Dulbecco's formula, containing 0.89 mmol Ca+2/L, pH 7.4). White blood cells were isolated by dextran sedimentation and hypotonic ammonium chloride lysis of the remaining erythrocytes. Granulocytes were further purified by centrifugation on sodium metrizoate (Lymphoprep). The cell preparations were finally resuspended in PBS. The purity of cell suspensions was determined by phase contrast microscopy. Platelet suspensions contained less than 1 granulocyte per 2 x 10^5 platelets, and granulocyte suspensions contained more than 98% granulocytes with a platelet contamination of less than 0.5 platelets per granulocyte.

Incubation procedure and product identification. All incubations (0.5 or 1.0 mL) were performed in duplicate at 37°C after 5 minutes of preincubation. Pure platelet suspensions (approximately 200 x 10^5 platelets/mL) were incubated for 30 minutes with LTA, in the presence of ionophore A23187 to study LX synthesis or with arachidonic acid to study 12-HETE and HHT formation. Platelet LT production was determined after incubation with LTA, for 5 minutes. Mixed suspensions of platelets and granulocytes (approximately 450 x 10^5 platelets and 15 x 10^5 granulocytes per mL) and white blood cell suspensions (15 x 10^5 leukocytes/mL with contaminating platelets) were incubated for 5 or 30 minutes with ionophore A23187 to study formation of LXs and LTs, respectively. LTA, arachidonic acid, and ionophore A23187 were used at 4, 75, and 1 pmol/L, respectively, unless otherwise indicated. Human serum albumin (0.3 mg/mL) was included in all incubations containing exogenous LTA,. The reactions were discontinued by the addition of 5 vol of ethanol. Cells from patients were always tested in parallel with cells from healthy controls.

After removal of precipitated material by centrifugation, the supernatant was evaporated, dissolved into appropriate mobile HPLC phase, and subjected to reverse phase HPLC. LXs were analyzed on an Ultrasphere-ODS column (4.6 x 250 mm; Beckman, San Ramon, CA) eluted with methanol/water/acetic acid (60:40:0.01, vol/vol/vol) at a flow rate of 1.0 mL/min. The identities of biosynthetic LXA, LXB, and 6(S)LXA were further confirmed by chrochromatography on a Nova-Pak C, Radial-Pak (5 x 100 mm; Waters Assoc, Milford, MA) eluted with acetonitrile/water/acetic acid (29:71:0.01, vol/vol/vol) at a flow rate of 0.1 mL/min. Analyses of HETEs and LTs were performed on a Nucleosil 120-3 C, column (3 x 100 mm; Macherey-Nagel, Düren, Germany) eluted with methanol/water/acetic acid (72:28:0.01, vol/vol/vol) or with acetonitrile/methanol/water/acetic acid (29:19:52:1, vol/vol, apparent pH 5.6), respectively, at a flow rate of 0.4 mL/min. On-line product quantitation was performed using a computerized diode array spectrophotometer (HP 8451A; Hewlett Packard, Los Angeles, CA) or a variable wavelength UV-detector (LDC Spectromonitor III; Laboratory Data Control, Stone, UK) connected to an integrator (LDC/Milton Roy IC-10B). Products were identified by cochromatography with synthetic standards and on-line UV spectroscopy. The following extinction coefficients were used for quantitation: LXs, 50,000; 12-HETE, 27,000; HHT, 33,400; LTB, and 5(S),12(S)- DHETE, 51,000; LTC, D, and E, 40,000. These systems permitted detection of LO products in the low picomolar range. The mean spread between duplicates was less than ±7%.

Statistics. Mean and standard error of the mean (SEM) were used as measures of location and spread. Comparison of groups of

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<th>Patient</th>
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<th>Age (yr)</th>
<th>Sex</th>
<th>Ph</th>
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<th>Ongoing Treatment*</th>
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<td>120-141</td>
<td>BU, --</td>
<td>0 → 112.8 → 0</td>
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*Platelets x 10^9/L blood at the time of test.
†Cytoreductive treatment at the time of or within 2 weeks before test.
‡Washed platelets (200 x 10^9/mL) were incubated with LTA, (4 μmol/L) and A23187 (1 μmol/L) for 30 minutes.
§Tested at five occasions during a 7-month period.

Abbreviations: CP, chronic phase; AP, accelerated phase; BC, blastic crisis; Ph, Philadelphia chromosome; BU, busulfan; α-IFN, α-interferon; HU, hydroxyurea.

Table 1. Clinical Characteristics and Platelet-Dependent LXA, Formation of Patients With CML
independent samples was performed using the Mann-Whitney U-test.

RESULTS

Conversion of exogenous LTA₄ to LXs and LTC₄ in platelet suspensions. Platelets from healthy volunteers consistently transformed LTA₄ to LXs, with LXA₄ as the major metabolite (438.7 ± 62.8 pmol LXA₄ per 10⁹ platelets; mean ± SEM, n = 14; see Fig 2A). In addition, 6(S)-LXA₄ and the all-trans isomers of lipoxins A₄ and B₄ were formed. A representative HPLC chromatogram obtained with normal platelets is displayed in Fig 1 (upper panel).

Platelets from the MPD patients showed a significantly decreased capacity to convert LTA₄ to LXs (157.4 ± 31.2 pmol LXA₄ per 10⁹ platelets; n = 24; P = .0001; Fig 2A). Six of the patients were in blastic crisis of CML. Platelets from all these individuals, but none of the others, displayed a markedly suppressed synthesis of LXs resulting in nondetectable amounts (n = 4) or less than 7% of mean control LXA₄ levels (n = 2). After exclusion of the blastic crisis patients from the MPD group, the mean LXA₄ formation was still significantly reduced (P = .0008). A chromatogram obtained with platelets from one of the CML patients in blastic crisis is shown in Fig 1 (lower panel). The peripheral platelet counts of the patients did not correlate with the ability to produce LXs in vitro (Table 1).

Formation of LTC₄ from LTA₄ was determined in platelet suspensions from two CML patients with deficient LX synthesis (producing nondetectable levels of LXs and 93.3 pmol LXA₄ per 10⁹ platelets, respectively). Both these patients readily converted LTA₄ to LTC₄ (1,156 and 873 pmol LTC₄ produced per 10⁹ platelets, respectively, as compared with a mean value of 933 ± 114 pmol LTC₄ per 10⁹ platelets in six healthy control subjects). The results indicate an intact LTC₄ synthase activity in the platelets of these CML patients.

Conversion of exogenous arachidonic acid to 12-HETE and HHT in platelet suspensions. The six CML patients in blastic crisis with severely impaired ability to form LXs also showed a dramatically decreased capacity to convert arachidonic acid to 12-HETE (2.5 ± 1.1 as compared with 81.5 ± 13.1 nmol 12-HETE per 10⁹ platelets in controls; n = 13; P = .0006). Representative chromatograms obtained with platelets from one of the CML patients in blastic crisis and one of the healthy controls are displayed in Fig 3. The mean 12-HETE formation of the entire MPD group (n = 22; Fig 2B) was moderately reduced (47.8 ± 13.9 nmol per 10⁹ platelets; P = .015). However, after exclusion of the patients with blastic crisis from the MPD group, the 12-HETE synthesis of the remaining patients was not significantly decreased (64.9 ± 17.4 nmol per 10⁹ platelets).

In contrast to the reduced 12-HETE formation, comparable amounts of HHT were formed in platelets from MPD patients in general, CML patients in blastic crisis, and controls (9.5 ± 1.6, 9.0 ± 3.1, and 7.9 ± 1.1 nmol HHT per 10⁹ platelets, respectively). This result suggests normal platelet prostaglandin endoperoxide synthase (formerly denoted cyclooxygenase) activities in the platelets from patients with MPD, including CML patients in blastic crisis.

Formation of lipoxigenase products by mixed cell suspensions. Ionophore A23187-stimulated mixed suspensions of normal platelets and granulocytes produced both LXA₄ and LXB₄ as well as LX isomers. In contrast, autologous platelet/granulocyte suspensions from two CML patients in chronic phase and one in accelerated phase produced markedly decreased or nondetectable amounts of LXs (Fig 4). However, when granulocytes from these patients were
Lipoxin formation and clinical characteristics of patients with CML in blastic crisis. Clinical characteristics and platelet LXA₄ formation of all CML patients are shown in Table 1. Six patients fulfilled the criteria of blastic crisis ("H" through "M"), all of the myeloid type. Four of these six patients were studied on repeated occasions during the course of the disease. The severely reduced capacity to synthesize LXs and 12-HETE was consistent irrespective of ongoing treatment or peripheral platelet counts. Five patients were studied at least once during blastic crisis at a time when no chemotherapy or NSAID medication had been taken for 2 weeks before testing.

Patient “H” was a woman first examined off treatment in chronic phase 1 year after diagnosis. She was studied a second time 7 months later after transformation to blastic crisis. At that time, the produced levels of LXs and 12-HETE were less than 3% of those obtained at the first examination, while the HHT formation remained unaltered.

Patient “I,” a 60-year-old woman, was studied on five occasions during a 7-month period. During this time, she gradually transformed from an accelerated phase, with migrating bone pains, increasing basophil counts, and progressive myelofibrosis, into an overt blastic crisis with predominance of myeloblasts and promyelocytes and additional chromosomal abnormalities (trisomy 8, isochromosome 17). Notably, the inability to form LXs and 12-HETE was present already in the accelerated phase and was consistent and reproducible throughout the entire study interval. On one occasion, the platelets were also incubated with a higher LTA₁ concentration (20 µmol/L), but still no LX formation could be detected.

The third patient, “J,” presented with a clinical picture of Ph-negative CML including a low LAP score, myelofibrosis, and loss of one chromosome 18. After 10 months of intermittent hydroxyurea treatment, she progressed into blastic crisis. Her platelets were analyzed 2 months later during on-going busulfan treatment (6 mg daily). Both LX and 12-HETE formation were below detection limits.

Patient “K,” a young male with a chemotherapy resistant blastic crisis, was studied twice over a period of 3 months. His platelets also showed a reproducible inability to synthesize both LXs and 12-HETE, while the capacity to transform arachidonic acid to HHT remained intact.

Patient “L” progressed into blastic crisis 8 years after CML was diagnosed. When studied off treatment shortly after metamorphosis, his platelets displayed a markedly decreased capacity to form LXs as well as 12-HETE.

The platelets of a 40-year-old male (patient “M”) were first studied during a newly diagnosed blastic crisis. At that time no conversion of LTA₁ to LXs could be observed and the 12-HETE formation was markedly reduced (Fig 5). After chemotherapy the patient entered a second chronic phase, during which the synthesis of LXs and 12-HETE was partially restored. When this patient returned into a second blastic crisis 2 months later, the LX/12-HETE formation was again strongly reduced. The synthesis of HHT was stable and within normal limits on all three occasions.
DEFICIENT PLATELET LIPOXIN SYNTHESIS IN MPD

![Graph showing the formation of LXA₄ and 12-HETE by platelets from a patient with CML](image)

**DISCUSSION**

The present report describes an impaired ability of platelets from patients with MPD, including CML, to synthesize LXs from LTA₄. This novel deficiency was particularly pronounced in blastic crisis of CML, as demonstrated by negligible or nondetectable LX formation. Partially reduced LX synthesis was also found in patients with PV and ET, indicating that decreased capacity to produce LXs may be a common platelet dysfunction in MPD.

The severely reduced LX production in platelets from CML patients with blastic crisis was paralleled by an almost abolished conversion of arachidonic acid to 12-HETE. In accordance, white blood cell suspensions (containing residual platelets) from these patients failed to produce the double dioxygenation product 5(S)12(S)-DHETE, while this compound constituted a major metabolite in control incubations. The findings reveal an abrogated 12-LO activity in platelets from CML patients in blastic crisis and provide further evidence for the involvement of this enzyme in LX formation. Previous findings indicate that partially deficient platelet 12-LO is a frequent phenomenon in MPD. In agreement, we observed a significantly reduced mean production of 12-HETE in MPD patients in general. However, although the platelet LX production was still significantly reduced in our remaining MPD patients (ie, results from patients in blastic crisis excluded) we were not able to clearly show a parallel impairment of 12-HETE formation in these patients. This discrepancy may be explained by the high concentration of arachidonic acid used in our experiments, because an excess of substrate may have masked a partial enzyme deficiency.

The finding of a close relation between severely deficient LX formation and blastic crisis of CML was convincingly supported also by longitudinal studies of individual patients. Thus, when one of the patients transformed from blastic crisis to a second chronic phase, a partial restoration of the capacity to synthesize LXs was observed. This capacity was again drastically reduced after retransformation into a second blastic crisis (Fig 5). In another patient, metamorphosis to blastic crisis was associated with an almost total suppression of LX formation.

Interestingly, the present results indicate deficient platelet LX production as an early sign of metamorphosis in CML. Thus, repeated investigations of platelets obtained from a patient during a gradual transformation from accelerated phase into blastic crisis displayed a constant inability to synthesize LXs.

Some of the platelet samples used in this investigation were collected from CML patients during ongoing chemotherapy. Drugs like busulfan, hydroxyurea, and α-interferon may theoretically affect the platelet LX formation. However, five of six patients in blastic crisis were also studied during chemotherapy-free intervals, and were then shown to have equally suppressed LX synthesis as under medication (Table 1). This finding indicates that the impaired LX formation is linked to disease-related mechanisms rather than to given cytotoxic drugs. In agreement, a previous report showed consistently low 12-LO activity in MPD platelets obtained before, during, or after busulfan medication.

In contrast to the reduced platelet 12-LO activity, other enzymatic capacities involved in eicosanoid metabolism appeared intact in platelets and leukocytes from MPD patients. Thus, a normal conversion of arachidonic acid to HHT was observed also in platelets from patients in blastic crisis. This result indicates an adequately retained platelet prostaglandin endoperoxide synthase pathway. Furthermore, because HHT and thromboxane (TX) A₂ are stoichiometrically formed by a common enzyme, the TX synthase, the results suggest an intact TX production in these platelets. In agreement, platelets from 15 out of 18 MPD patients with deficient 12-LO were reported to produce normal and equimolar amounts of HHT and TXB₂. An intact 5-LO pathway in leukocytes was indicated by the finding present of normal or increased ionophore-induced LT synthesis in white blood cell suspensions from patients with blastic crisis. These results are in agreement with our earlier findings of an increased capacity of CML leukocytes to produce LTC₄ and indicates an active platelet LTC₄ synthase. A retained ability of CML granulocytes to release LTA₄ was also demonstrated, because normal amounts of LXs were formed in mixed incubations with these granulocytes and control platelets (Fig 4). Finally, the production of LXB₄ in these incubations suggests that the CML granulocytes expressed the epoxide hydrolase activity, necessary for formation of this compound.

MPD are characterized by a clonal disturbance of hematopoietic stem cells, typically manifested not only in myelopoietic cells, but also in megakaryocytes and platelets. Thus, a variety of morphologic and functional platelet abnormalities have been described, eg, macrothromboocytes, increased content of platelet factor 4 and β-thromboglobulin, both increased and decreased aggregation responses, reduced ATP secretion, etc. However, none of these in vitro abnormalities have been convincingly correlated to in vivo clinical complications, like bleedings or thrombotic events. Although it was suggested that 12-LO-deficient platelets may show an increased TX formation and facilitation of in vitro aggregation, this has not been...
satisfactorily confirmed clinically by an elevated incidence of thrombosis.

Deficient platelet 12-LO activity has previously been documented in MPD.13-15 The present investigation extends these findings and demonstrates an essentially abolished 12-LO in platelets from CML patients in blastic crisis. The physiologic importance of 12-LO has been considered uncertain, because the biologic role of the classical products, 12-H(PE)TE and 12-HETE, is unclear. However, the finding that the platelet 12-LO possesses the capacity to produce LXs may suggest a new role for this enzyme.12 Therefore, the functional relevance of a defect platelet 12-LO may be related to the biologic activities of the LXs rather than to those of 12-H(PE)TE. We have previously shown a strongly increased capacity of leukocytes and purified granulocytes from CML patients to produce LTA4. Interestingly, this compound, as well as LTBl, has been reported to stimulate human and murine myelopoiesis in vitro.20,29 A role for LTs in hematopoiesis in vivo was suggested by a recent report showing a distinct increase in urinary cysteinyl-containing LTs in cytopenic patients after administration of the hematopoietic growth factor granulocytemacrophage colony-stimulating factor.29 It is possible that interactions between platelets normally present in large quantities in the bone marrow and myeloid cells under certain circumstances lead to production of LXs in vivo. In this context, the reported antagonistic effects of LXA4 and LXB4 on LT-induced biologic events5,5 are of special interest. Thus, the LXs may exert a regulatory effect on LTC4-stimulated proliferation of myeloidopoietic stem cells. Therefore, it is tempting to speculate that a deficient LX formation may be of relevance for the uncontrolled myelopoiesis associated with MPD in general and blastic crisis of CML in particular. Furthermore, the inadequate 12-LO activity in MPD leads to decreased production of the transcellularly formed 5(S), 12(S)-DHETE,19 a substance reported to inhibit LTBl-stimulated myelopoiesis.30 The effect of LXs on human myelopoiesis in normal and leukemic bone marrow is currently under investigation.

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Deficient lipoxin synthesis: a novel platelet dysfunction in myeloproliferative disorders with special reference to blastic crisis of chronic myelogenous leukemia

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