Decreased Arachidonic Acid Release in Peripheral Blood Monocytes of Patients with Systemic Lupus Erythematosus

SÁNDOR SIPKA, SÁNDOR SZÁNTÓ, KORNÉLIA SZŰCS, ILDIKÓ KOVÁCS, EMESE KISS, PÉTER ANTAL-SZALMÁS, GABRIELLA LAKOS, MAGDOLNA ALEKSZA, ÁRPÁD ILLÉS, PÁL GERGELY, and GYULA SZEGEDI

ABSTRACT. ***Objective.*** To investigate the release of arachidonic acid (AA) in unfractionated peripheral blood mononuclear cells (PBMC), separated monocytes and T lymphocytes of patients with systemic lupus erythematosus (SLE).

Methods. AA release was measured in cells from 56 patients with SLE and from 48 controls. Of the 56 patients with SLE, 38 were receiving glucocorticosteroids and 18 were not. [^{3}H]AA was incorporated into the membranes of PBMC and purified subsets of monocytes and T lymphocytes. The release of [^{3}H]AA was measured both in nonstimulated cells cultured for 24 h and in cell cultures stimulated by phorbol ester (PMA) and Ca^{2+} ionophore for 4 h.

Results. In the PBMC of SLE patients not taking glucocorticosteroids, the release of AA was decreased in both stimulated and nonstimulated cells. There was a decrease of AA production in monocytes but not in T lymphocytes. This phenomenon could be observed in the active and inactive phases of the disease.

Conclusion. A defect in AA production may exist in the peripheral monocytes of patients with SLE, resulting in decreased release of AA in patients not receiving glucocorticosteroid therapy. (J Rheumatol 2001;28:2012–7)

Key Indexing Terms:
SYSTEMIC LUPUS ERYTHEMATOSUS MONOCYTES ARACHIDONIC ACID

Systemic lupus erythematosus (SLE) is an autoimmune syndrome characterized by disordered cellular and humoral immune responses leading to pathologic autoantibody production. In the pathomechanism of the disease, a complex multicellular dysfunction of all mononuclear leukocytes, including monocytes/macrophages, natural killer cells, and B and T lymphocytes is involved[1]. In explanation of the T cell defects at the level of signal transduction, decreased protein kinase C activity[2], diminished levels of protein kinase A RIα and RIβ transcripts and proteins, and the disturbance of cAMP metabolism have been described[3-5]. Further, abnormal nuclear factor κB (NF-κB) activity and decreased p65-RelA protein expression have been reported[6].

The types of abnormalities described in the monocytes of patients with SLE can be divided into 3 groups. First, a decrease in chemotaxis[7], phagocytic activity[8-11], expression of HLA-DR[12], CD14[13], and Fc gamma receptors type II and III[14] can be mentioned. Second, decreased production of leukotriene B4[15], eicosanoids[16], superoxide anions[14], interleukin 1 (IL-1β)[17], and IL-12[18] can be listed. Third, increased production of procoagulant factor[19], C3[20], soluble CD14[21], and IL-1 receptor antagonist[22] can be involved.

Arachidonic acid (AA) is not only the precursor molecule of prostaglandins, thromboxanes, and leukotrienes but it also regulates a number of signal transducing elements, including phospholipase C, sphingomyelinase, and certain protein kinase isoforms such as PKC α, β, and γ[23-25]. Further, AA can modulate the nuclear translocation of NF-κB[26]. The actual level of AA is mainly dependent on the activity and interaction of 3 intracellular enzymes: cytosolic phospholipase A_2 ($cPLA_2$, type IV), Ca^{2+} independent phospholipase A_2 ($iPLA_2$, type VI), and diacylglycerol (DAG) lipase[27].

From the 3rd Department of Internal Medicine and the Department of Medical Chemistry, Medical and Health Science Centre, University of Debrecen, Debrecen, Hungary.

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S. Sipka, MD, PhD, DSci, Professor of Laboratory Science; S. Szántó, MD, Fellow in Rheumatology; I. Kovács, Research Technician; E. Kiss, MD, PhD, Associate Professor of Medicine; G. Lakos, MD, PhD, Assistant Professor of Laboratory Science; P. Antal-Szalmás, MD, PhD, Assistant Professor in Laboratory Science; M. Aleksza, PhD Student; Á. Illés, MD, PhD, Associate Professor of Medicine; G. Szegedi, MD, PhD, DSci, Professor of Medicine, 3rd Department of Internal Medicine; K. Szűcs, Associate Professor in Medical Chemistry; P. Gergely, PhD, DSci, Professor of Medical Chemistry, Department of Medical Chemistry, Medical and Health Science Centre.

Address reprint requests to Dr. S. Sipka, 3rd Department of Internal Medicine, Medical and Health Science Centre, University of Debrecen, H-4004 Debrecen, Hungary. E-mail: sipka@iiibel.dote.hu

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Earlier observations described damage in the synthesis of leukotriene B_4 [15], eicosanoids, prostaglandin E_2, and thromboxane B_2 [16] in the monocytes of patients with SLE. Thus, the release of AA, a precursor of these biologically active compounds, was investigated in peripheral blood mononuclear cells (PBMC) and in separated monocytes and T cells of SLE patients and healthy controls in this study. The effects of inhibitors of the enzymes involved in AA release of mononuclear cells[28] were also analyzed.

MATERIALS AND METHODS

Patient and control populations, and clinical data. The SLE study population consisted of 56 patients, 46 women and 10 men, average age 43 years, range 18–69 years. The mean SLE Disease Activity Index (SLEDAI) rating was 5.9, range 2–20. The average amount of glucocorticosteroid (methylprednisolone or prednisolone equivalent) taken by the patients was 10.8 mg/day, range 0–32 mg/day. The average duration of disease was 8.5 years, range 0.5–41 years. All patients fulfilled at least 4 of the revised criteria for the classification of SLE[29]. The actual activity of the disease was scored according to SLEDAI[30]. Patients with SLEDAI score ≤ 3 were considered to have inactive disease. Three subgroups of these patients were studied: (1) 18 patients without steroid therapy, 14 women and 4 men, average age 42 years, mean SLEDAI score 4.5; (2) 24 patients taking 4–12 mg steroid/day, 21 women and 3 men, average age 43 years, range 18–57 years, mean SLEDAI 5.3; (3) 14 patients taking 16–32 mg steroid/day, 12 women and 2 men, average age 32 years, mean SLEDAI 9.8. As controls, 48 healthy Caucasian subjects (34 women, 14 men, average age 38 yrs, range 20–52 yrs) were studied. The SLE patients were treated only with steroids and did not take cytostatic drugs during the study period.

Approval was given through the Institutional Review Board, and informed consent was obtained from all participants.

Preparation of human PBMC and characterization by flow cytometry. Unfractionated PBMC (88–95% lymphocytes and 5–12% monocytes) were prepared from the peripheral blood of SLE patients and healthy controls according to the method of Boyum[31]. The averages of the various cellular subsets were detected by flow cytometry: CD3+ 69.4%, CD19+ 11.5%, CD56+ 10.8%, and CD14+ 8.3. There was no significant difference in the ratios of subsets in the PBMC of SLE patients and controls. The suspensions of mononuclear cells (10^6 cells per sample) were labeled by saturating concentrations of anti-CD3-FITC (T3, Coulter, Hialeah, FL, USA), anti-CD19-RD1 (B4, Coulter), anti-CD56-PE (Leu-19, Becton-Dickinson, Mountain View, CA, USA), and anti-CD14-RD1 (MY4, Coulter) monoclonal antibodies. After staining and fixing, the cells were analyzed by a Coulter EPICS XL flow cytometer.

Preparation of purified subsets of monocytes and T cells. The Dynal magnetic bead cell separation technique was used[32]. The average monocyte purity was > 90%; the average T cell purity was > 95%.

Measurement of arachidonic acid release. The cells (10^5/ml) were preincubated with [^{3}H]AA (Amersham, UK) in a CO_2 incubator at 37˚C for 20 h. After extensive washing, the cells were further incubated with no stimuli for 4 h. The released [^{3}H]AA reflected the basal activity of the intracellular enzymes involved in the production of AA[27]. The activation of $cPLA_2$ and other enzymes producing AA was achieved by the addition of 5 μmol of calcium ionophore (A23187, Sigma, St. Louis, MO, USA) and 50 ng/ml of PMA (phorbol 12-myristate 13-acetate; Sigma) in the 20th hour of culturing at 37˚C[33] for 4 h. This amount of released [^{3}H]AA reflects the total activity of the intracellular enzymes releasing AA in the stimulated cells. Each value was calculated as the average of triplicates of cultured cells.

Inhibition of arachidonic acid release by enzyme inhibitors. 100 μM of arachidonyl trifluoromethyl ketone (AACOF3, the inhibitor of $cPLA_2$), 10 μM of palmitoyl trifluoromethyl ketone (PACOCF3, inhibitor of $iPLA_2$), and 10 μM of RHC-80267 (inhibitor of DAG lipase) were added to the cells 15 min before addition of PMA + Ca^{2+} ionophore. The percentage of inhibition was calculated by the comparison of AA values in the supernatants of cells cultured in the absence or presence of inhibitors. Enzyme inhibitors were purchased from Calbiochem (Switzerland).

Statistical analysis. The statistical means and standard deviation (SD) values were calculated. To compare the data of patients and controls the statistical significance of the differences was determined by Student's unpaired t test. Student's paired t test was used in the self-control experiments. A value of $p < 0.05$ was considered significant.

RESULTS

AA release in PBMC of patients and controls. AA release (mean ± SD) was decreased in both nonstimulated (3425 ± 502 vs 4652 ± 659 dpm; $p < 0.05$) and stimulated (7391 ± 922 vs 9546 ± 1211 dpm; $p < 0.05$) cells of steroid-free SLE patients compared to the values of healthy controls. On the other hand, the AA release was more pronounced in patients treated with low (4–12 mg/day) or high (16–32 mg/day) doses of steroid than in the steroid-free group of patients (Figure 1). The AA release measured in the group of patients with high steroid doses was slightly, but not significantly, higher than in the controls (4875 ± 612 vs 4652 ± 659 dpm in nonstimulated cells, and 9802 ± 1022 vs 9546 ± 1211 dpm in stimulated cells). It should be mentioned that patients treated with high steroid doses (16–32 mg/day) were in an active phase of the disease and required elevated amounts of steroid.

AA release in PBMC of steroid-free patients with active and inactive disease. In the group of 18 steroid-free SLE patients, 7 could be regarded as "new cases," with an average SLEDAI index of 6.5. These 7 patients were on the verge of beginning steroid therapy. The other 11 patients had already been treated with steroids for several years. The average of their SLEDAI scores was 2.57. During the study period they were in the inactive phase of disease and were not receiving steroids or other drug therapy. As shown in Figure 2, there was no difference in the release of AA between patients with inactive or active SLE either in nonstimulated (3516 ± 637 vs 3335 ± 612 dpm) or in stimulated cells (7561 ± 847 vs 7228 ± 1042 dpm). The data of 48 healthy controls are also presented to show that amounts of AA released by the cells of patients with active or inactive SLE were lower in both nonstimulated and stimulated cultures (3516 ± 637, 3335 ± 612 vs 4652 ± 659 dpm in nonstimulated cells, $p < 0.05$; and 7561 ± 847, 7228 ± 1042 vs 9546 ± 1211 dpm, $p < 0.05$ and $p < 0.05$ in the stimulated cells).

Release of AA in PBMC, purified monocytes, and T cells in patients and controls. The release of AA in the PBMC and in the purified monocytes and T cells of 10 healthy controls and 15 SLE patients (10 steroid-free, SLEDAI score 3.9, and 5 taking 4 mg/day steroid, SLEDAI 4.6) was compared (Figure 3A). Stimulation by PMA alone resulted in a significant increase of AA release in the PBMC of controls compared to SLE patients (6316 ± 759 vs 3792 ± 629 dpm; p <

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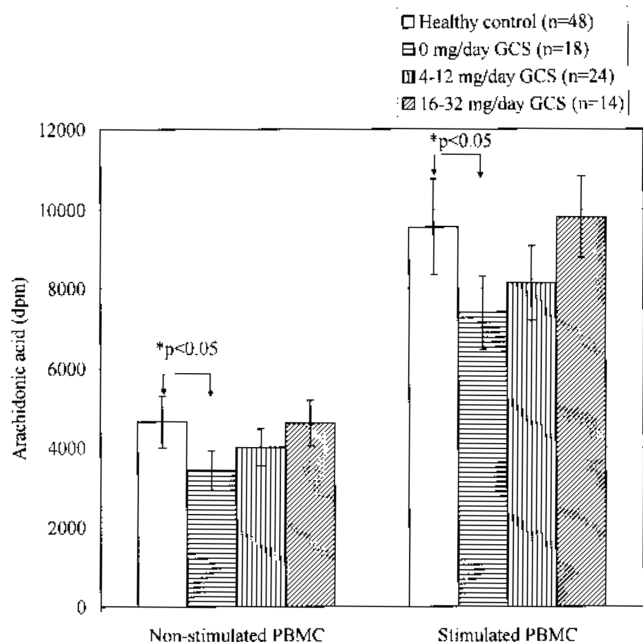

Figure 1. Release of arachidonic acid in PBMC of SLE patients taking various doses of glucocorticosteroids and in healthy controls. SLE patients without steroid therapy, n = 18; SLE patients taking 4–12 mg steroid/day, n = 24; SLE patients taking 16–32 mg steroid/day, n = 14. Controls, n = 48. Each bar represents mean ± SD. *p < 0.05.

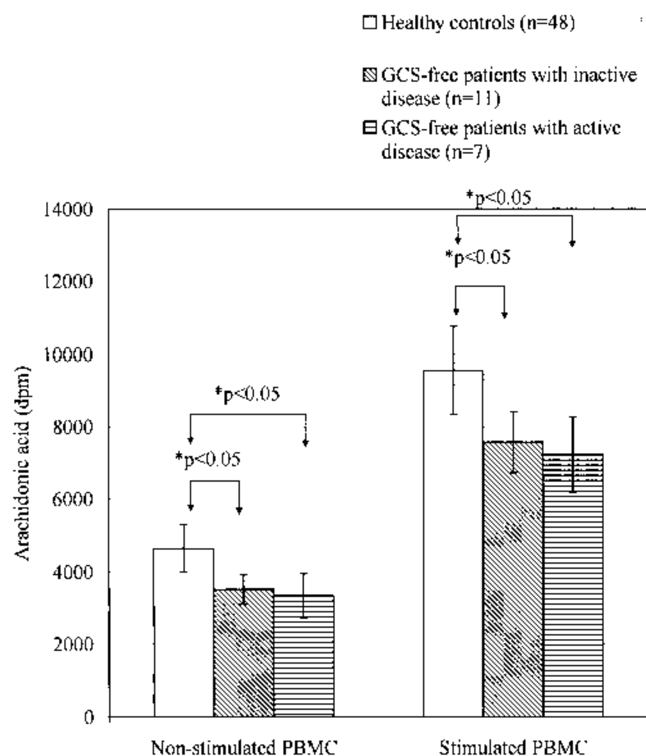

Figure 2. Release of arachidonic acid in PBMC of glucocorticosteroid–free SLE patients in inactive and active states of the disease and in controls. Patients with inactive disease, n = 11; with active disease, n = 7. Controls, n = 48. Each bar represents mean ± SD. *p < 0.05.

0.01). In controls, PMA significantly elevated the release of AA compared to nonstimulated cells (6316 ± 759 vs 4019 ± 562 dpm; p < 0.01). On the other hand, PMA induced only a nonsignificant elevation of AA release compared to nonstimulated cells of SLE patients (3792 ± 629 vs 3116 ± 415 dpm). The stimulation of cells by PMA + Ca^{2+} ionophore yielded almost similar elevations of AA release in both patients and controls compared to the effect of PMA applied alone (PMA, 3792 ± 629 dpm, PMA + Ca^{2+} ionophore, 6456 ± 891 dpm. Elevation 2664 dpm in SLE patients; PMA, 6316 ± 759 dpm, PMA + Ca^{2+} ionophore, 8563 ± 1241 dpm; elevation 2247 dpm in controls). The significantly decreased release of AA by PMA + Ca^{2+} ionophore stimulated PBMC of SLE patients compared to controls in these experiments could also be observed (6456 ± 891 vs 8563 ± 1241 dpm; p < 0.05).

There was a great difference in the AA release of purified monocytes and T cells (Figure 3B) compared to values measured in PBMC of the same donors (Figure 3A). The monocytes of healthy controls produced an elevated release of AA by stimulation of PMA + Ca^{2+} ionophore, whereas the monocytes of patients did not respond to this stimulation (956 ± 195 vs 459 ± 131 dpm; p < 0.01). On the other hand, T cells from controls or patients did not show this effect. In both types of purified cells, PMA alone did not result in any elevation of AA release. However, the value in the nonstimulated monocytes of patients was lower than in the controls (412 ± 110 vs 716 ± 145 dpm; p < 0.05). PMA alone caused a slight but not significant reduction in the AA release compared to the values of the nontreated cells.

Effect of phospholipases A_2 and DAG lipase inhibitors on AA release in PBMC of patients and controls. The inhibitors AACOF3 for $cPLA_2$, PACOCF3 for $iPLA_2$, and RHC-80267 for DAG lipase were used to determine the contribution of these enzymes to AA release of PBMC stimulated by PMA + Ca^{2+} ionophore in 7 SLE patients (5 steroid-free, 2 taking 8 mg steroid/day) and in 7 healthy controls. The inhibitors of $cPLA_2$ and $iPLA_2$ resulted in similar inhibition (26 and 29%) of the controls, whereas the inhibitor of DAG lipase had no effect (Figure 4). In patients, the same concentration of $iPLA_2$ inhibitor reduced the release of AA by 43%, the inhibitor of $cPLA_2$ by 19%, and the inhibitor of DAG lipase by 11%. (The measurements could be carried out with rather large SD values.) There was no difference in the data from steroid-free patients and those taking 8 mg steroid/day. The results suggested that in the release of AA in the stimulated PBMC of SLE patients, $iPLA_2$ might play a more important role than $cPLA_2$, and DAG lipase might also contribute to the production of AA in SLE. However, no definitive conclusion could be drawn from these results because of the lack of statistical significance in the changes caused by the inhibitory drugs.

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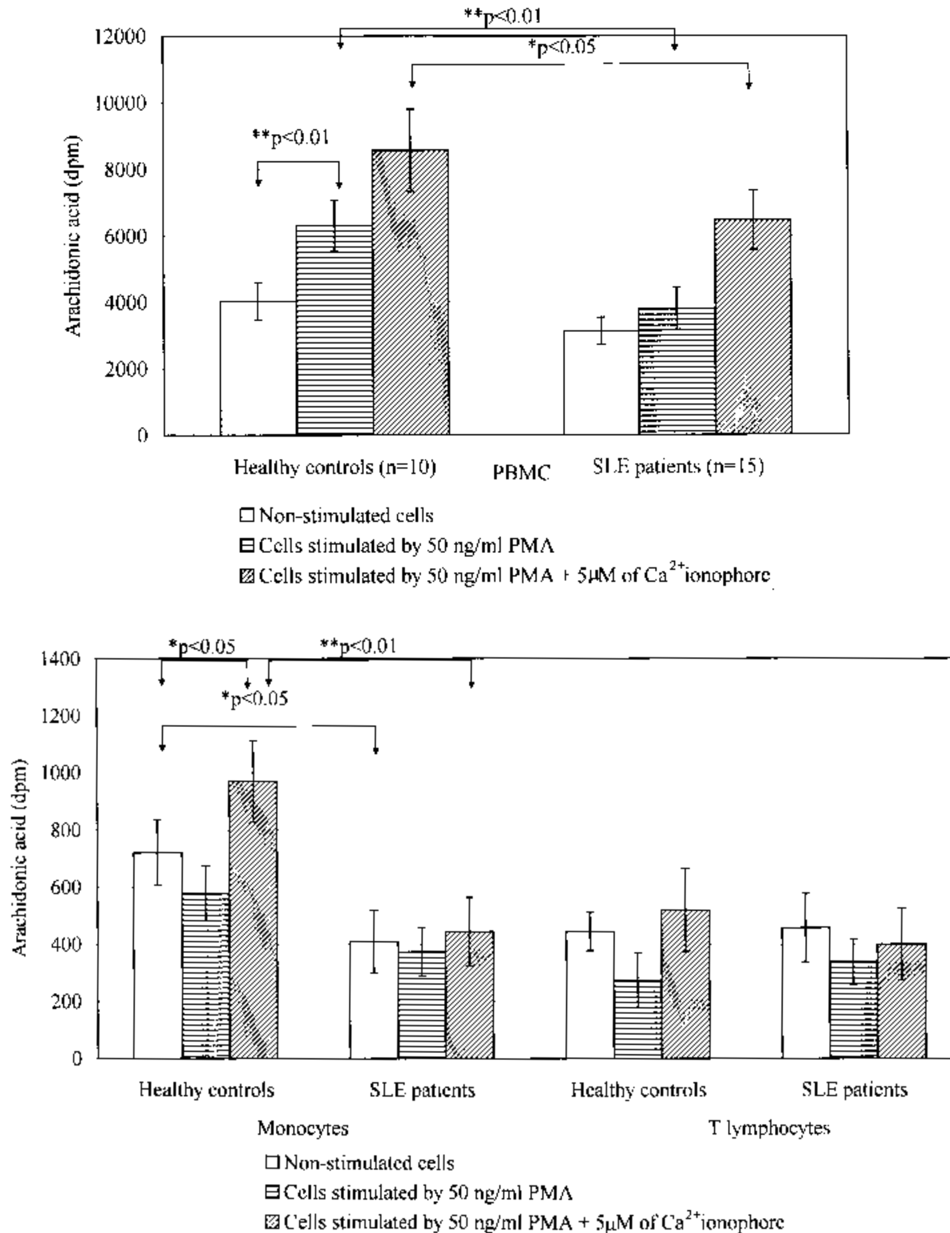

Figure 3. PMA and PMA + Ca^{2+} ionophore induced release of arachidonic acid (A) in PBMC and (B) in purified suspensions of monocytes or T lymphocytes of SLE patients and controls. SLE patients, n = 15 (10 steroid-free, 5 taking 4 mg steroid/day). Controls, n = 10. Each bar represents mean ± SD. *p < 0. 05, **p < 0.01.

DISCUSSION

According to our data the production and release of AA were decreased in both nonstimulated and stimulated PBMC of steroid-free patients with SLE. On the other hand, in patients taking 16–32 mg/day doses of corticosteroids, the release of AA was the same as or even slightly higher than that of the healthy controls. One could suggest that some defect of AA production exists in the PBMC of SLE patients. In addition, the high dose of steroids could modify the actual release of AA from these cells. The impaired AA release seemed to be independent of the activity or inactivity of the disease. As 7 steroid-free patients were in the active phase of the disease and 11 were in the inactive phase, the number of active cases was rather low. It is interesting that decreased AA release was not detected in other polysystemic autoimmune diseases (e.g., in some steroid-free patients with mixed connective tissue disease and primary Sjögren's syndrome; unpublished data), suggesting that the

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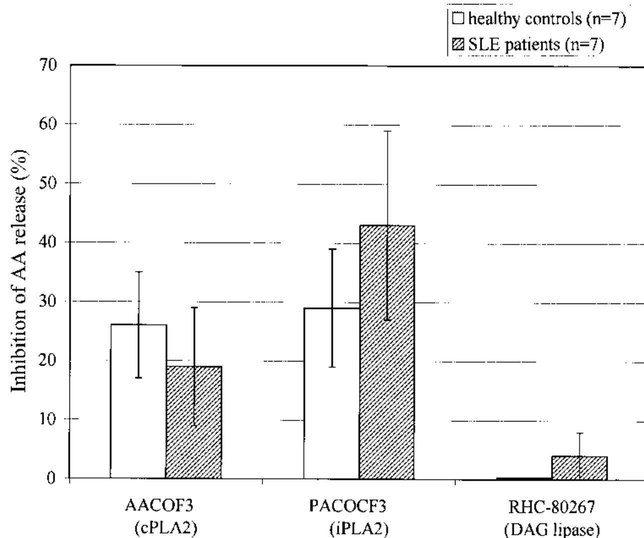

Figure 4. Effect of the inhibitors of phospholipases A_2 and DAG lipase on the release of arachidonic acid in PBMC stimulated by PMA + Ca^{2+} ionophore in SLE patients and controls. SLE patients, n = 7 (5 steroid-free, 2 taking 8 mg steroid/day). Healthy controls, n = 7. AACOF3: arachidonyl trifluoromethyl ketone, inhibitor of $cPLA_2$ (100 μM); PACOCF3: palmitoyl trifluoromethyl ketone, inhibitor of $iPLA_2$ (10 μM); RHC-80267: inhibitor of DAG lipase (10 μM). Each bar represents mean ± SD. Inhibitions are expressed in percentages caused by the agents compared to control values (without inhibitors).

observed impairment of AA release could be specific for SLE. Monocytes and T cells were separated by magnetic beads from PBMC to verify that monocytes and not T cells of SLE patients were involved in the defect of AA release. Whereas the monocytes of healthy controls stimulated by PMA + Ca^{2+} ionophore could produce increased amounts of AA, the monocytes of SLE patients were not able to do this. In T cells, the induction of AA release was limited both in controls and in patients with SLE. This finding confirmed the observation regarding the lack of $cPLA_2$ activity in mature human T and B cells[34]. In the supernatants of PBMC the amount of AA was almost 10 times greater than in the purified cells. It is also of interest that PMA alone caused a significantly higher release of AA in the PBMC of controls than in patients, suggesting some role of DAG related pathways in this impaired regulation. The stimulation of these cells by PMA + Ca^{2+} ionophore, however, increased the production of AA to almost the same extent in the 2 groups of subjects, suggesting the lack of difference in the Ca^{2+} mediated signal pathways. We could give 2 possible explanations for the differences of AA release in PBMC and purified cells. During the labeling of PBMC by [^{3}H]AA and culturing the cells for 24 h, considerable amounts of IL-1, tumor necrosis factor-α, and other cytokines could be produced by the influence of the contact of attached cells to the surface of the plates[35]. These cytokines, mainly IL-1, could stimulate the activity of PLA_2 enzymes[36]. Thus, in a cytokine-rich medium the "second signal" effects of PMA and its combination with Ca^{2+} ionophore could result in significant elevations in the activities of AA producing enzymes. The other possibility could be that both monocytes and T cells became functionally damaged with regard to AA production during the purification procedure by magnetic beads. This damage could be observed in the cytokine production and in the response of cells to stimulation by PMA and/or PMA + Ca^{2+} ionophore, but it was not reflected in the release of lactate dehydrogenase, a test used for the demonstration of cell viability (unpublished data). These experiments, however, showed clearly that monocytes and not T cells were the sources of diminished AA release in the PBMC of SLE patients.

According to the results with the enzyme inhibitors, all the 3 enzymes, $cPLA_2$, $iPLA_2$, and DAG lipase, might be involved in AA release from PBMC. However, the extent of their role should be determined more exactly[24].

In our results, observation of impaired AA release in the monocytes of SLE patients was in accord with observations of decreased production of prostaglandins and leukotrienes by these cells[15,16]. According to our data, PMA, a molecule activating protein kinase C, had less effect on the monocytes of SLE patients than on those of controls. We suppose that the defect of protein kinase C described for T cells[2] might also exist in monocytes. It is also possible that the decreased capacity of monocytes to produce and release AA could contribute to the limited capability of these cells to express Fc receptors[13], leading to the inadequate clearance of immunocomplexes in SLE.

The difference in the AA production of steroid-free SLE patients and those treated with higher doses of steroids could possibly be explained by the apoptosis inducing effect of steroids in these subjects[37]. In mononuclear cells of higher apoptotic rate, however, the activation of $iPLA_2$ could take place, resulting in increased production of AA by $iPLA_2$ [38]. The latter could be responsible for the significantly increased AA release in the PBMC of patients treated with 16–32 mg/day doses of steroids compared to the steroid-free subjects. This hypothesis, however, requires confirmation.

The defect in the release/diminished release of AA by the monocytes of patients with SLE can explain some earlier findings on the impaired function of phagocytes in this disease. Further studies are required to elucidate the mechanism of this damaged, possibly protein kinase C dependent, pathway of AA metabolism.

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