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Serum Phospholipases A_2 in Patients Undergoing Panproctocolectomy Because of Severe Ulcerative Colitis[1])

Markku M. Haapamäki[1], *Juha M. Grönroos*[1], *Erkki Pekkala*[1], *Anne Jokilammi-Siltanen*[2], *Kerttu Irjala*[3], *Kalle Lertola*[4] and *Timo J. Nevalainen*[2]

[1] Department of Surgery, University of Turku, Turku, Finland
[2] Department of Pathology, University of Turku, Turku, Finland
[3] Central Laboratory, Turku University Central Hospital, Turku, Finland
[4] Department of Statistics, University of Turku, Turku, Finland

Summary: A major role has been proposed for group II phospholipase A_2 in the pathogenesis of local and generalised inflammatory reactions. Elevated catalytic activity and mass concentrations of this enzyme have been found in serum and tissue samples of the colon in patients with active ulcerative colitis. The cellular source(s) of group II phospholipase A_2 in the blood circulation is (are) unknown. In the current prospective study, we investigated the mass concentration of group II phospholipase A_2 and the catalytic activity concentration of phospholipase A_2 in serial serum samples of 15 consecutive patients who underwent a standard panproctocolectomy operation for severe ulcerative colitis. Both the catalytic activity concentrations of phospholipase A_2 and the mass concentrations of group II phospholipase A_2 increased rapidly in serum samples to maximum values on the first postoperative day and then decreased ($p = 0.002$ and $p < 0.001$, respectively) in patients who recovered uneventfully. Three patients had postoperative complications that further increased the enzyme concentrations at the time of respective complications. The pattern of group II phospholipase A_2 mass concentration profiles was similar to the profiles of C-reactive protein. The results show that the removal of the large bowel does not eliminate the potential to secrete group II phospholipase A_2 into the blood circulation in these patients. Secretion of group II phospholipase A_2 into the circulation after surgery seems to be a normal host response to a major abdominal operation and postoperative complications. Consequently, we conclude that the large bowel is not an important source of group II phospholipase A_2 in sera of patients with ulcerative colitis. The results also support the assumptions that the catalytic activity of phospholipase A_2 in serum is attributable to group II phospholipase A_2 and that this enzyme is an acute phase protein.

Introduction

Phospholipase A_2[2]) hydrolyses the fatty acyl ester bond at the *sn*-2 position of glycerophospholipids. The enzyme is widespread in bacteria, plants, snake and bee venoms, mammalian cells, and secretions (1, 2). Phospholipase A_2 has been implicated in the pathology of various inflammatory diseases including infections, sepsis, various arthritides, *Crohn*'s disease and ulcerative colitis (3).

Secretory phospholipases A_2 are divided into several groups on the basis of the amino acid sequence of the enzyme (4, 5). Group I and II phospholipases A_2 are present in human tissues, have high disulphide bond content, low molecular mass (14000 M_r) and require millimolar concentrations of Ca^{2+} for catalysis. Group I phospholipase A_2 originates from pancreatic acinar cells and serves mainly as a digestive enzyme. Group II phospholipase A_2 is found in several cells and tissues such as articular cartilage (6, 7), *Paneth* cells of the small intestinal mucosa (8, 9), the amnionic epithelial cells of fetal membranes (10) and the gland cells of the prostate (11) or extracellularly when released in response to pro-inflammatory mediators such as interleukin-1, interleukin-6 or tumour necrosis factor (12, 13). The mass concentration of group II phospholipase A_2 and catalytic activity concentration of phospholipase A_2 are notably increased in sera of patients with inflammatory diseases (14) including inflammatory bowel diseases (15). A major role has been proposed for group II phospholipase A_2 in the pathogenesis of local and generalised inflammatory reactions. The cellular source(s) of group II phospholipase A_2 found in the circulation is (are) unknown. We have recently shown group II phospholipase A_2 gene expression and group II phospholipase A_2 protein in metaplastic *Paneth* cells and in epithelial cells in the mucosa of inflamed large intestine in ulcerative coli-

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[2]) Enzyme:
Phospholipase A_2, phosphatide 2-acylhydrolase (EC 3.1.1.4)

tis (9). Against this background, the inflamed colon might be a source of circulating group II phospholipase A_2 in patients with active drug-resistant ulcerative colitis, as suggested in a recent report (16).

The purpose of the present work was to study the effect of panproctocolectomy on the catalytic activity concentration of phospholipase A_2 and the mass concentration of group II phospholipase A_2 in serum in ulcerative colitis. The mass concentration of group I phospholipase A_2 was measured to rule out pancreatic involvement in a possible postoperative increase in the catalytic activities of phospholipase A_2. The mass concentration of C-reactive protein was measured to detect postoperative complications and also for comparison between this classic acute phase reactant and the phospholipase A_2 measurements. The results show that panproctocolectomy does not result in the disappearance of group II phospholipase A_2 from serum of patients with ulcerative colitis.

Materials and Methods

Patients

Fifteen consecutive patients operated for ulcerative colitis at the University Central Hospital of Turku were enrolled in the present prospective study. There were nine men and six women; the mean age of the patients was 40 years (range 22 to 70 years). The average length of the disease history was 10 years and six months (range 10 months to 28 years). All patients were operated for active and drug resistant ulcerative colitis and one patient had dysplastic changes in the colonic mucosa before the operation. Thirteen patients received oral prednisone (range 5 to 80 mg/day) preoperatively and these patients were given intravenous hydrocortisone (range 100 to 200 mg/day) or methylprednisolone (range 80 to 125 mg/day) during the recovery period. The corticosteroid doses were gradually decreased to preoperative levels and oral medication was started on the 5^{th} to 14^{th} postoperative day depending on the patient's general condition and bowel function. The corticosteroid therapy was discontinued one to three months after the operation. Nine patients received 5-aminosalicylic acid (range 1200 to 3600 mg/day), five patients received salazosulphapyridine (range 3000 to 4500 mg/day) and three patients received antibiotics before the operation. All patients received systemic prophylactic therapy with cefuroxim (2250 mg/day) and metronidazole (1500 mg/day) during five postoperative days. Two men and one woman were excluded from the statistical analysis due to complications during the recovery period, since we assume that early complications may affect the measurements of interest. One of the excluded men had a short period of acute respiratory insufficiency on the third postoperative day and was treated in the intensive care unit, and the other man had pneumonia diagnosed on the seventh postoperative day. The female patient excluded had a postoperative intestinal obstruction and was reoperated on the seventh day after the panproctocolectomy. Eleven of the statistically analysed 12 patients were on prednisone therapy for ulcerative colitis. The control group consisted of 27 age- and sex-matched healthy blood donors. There were 17 men and 10 women and the mean age was 42 years (range 21 to 64) in the control group. The study was approved by the local ethics committee and an informed consent was obtained from each patient.

Operation

All the patients underwent a standard panproctocolectomy operation during general anaesthesia. The operation involved an ileoanal anastomosis with a J-pouch in ten cases and a conventional ileostomy in five cases. The mean operation time was 200 minutes (range 160 to 225). The mean blood loss during the operations was 1280 ml (range 350 to 3200). The blood volume was maintained with infusions of isotonic electrolyte solutions, and packed red blood cells were given to maintain the blood haemoglobin concentration above 100 g/l. Twelve patients recovered uneventfully and three patients had postoperative complications as described above.

Blood samples

Blood samples were collected in the morning before the operation and daily thereafter until the seventh postoperative day. An additional blood sample was taken at the routine follow-up examination about three months after the operation. Serum was separated and stored at −20 °C until assayed. The mass concentrations of group I phospholipase A_2 and group II phospholipase A_2, the catalytic activity concentration of phospholipase A_2 and the mass concentration of C-reactive protein were measured. The mass concentrations of group I and group II phospholipases A_2 were analysed by time-resolved fluoroimmunoassays (17, 18), the catalytic activity concentration of phospholipase A_2 was assayed by using micellar radioactive phosphatidylcholine as a substrate (19), and the mass concentration of C-reactive protein by immunoturbidimetry (standard and antiserum from Orion Diagnostica, Espoo, Finland). Blood samples of the control group were collected by taking 10 ml blood from 27 healthy donors during routine blood donations.

Statistical analysis

The results are expressed as mean and standard error of mean (±SEM) for the 12 patients who recovered uneventfully, and as case profiles for the three patients with postoperative complications. The statistical analysis for repeated measurements was carried out using analysis of variance in the SAS system MIXED procedure (version 6.11). The model is based on the restricted maximum likelihood estimation method, one between factor, and unstructured covariance structure. Contrasts were used to compare differences between time points. The t-test for independent samples was used to compare preoperative and late postoperative group II phospholipase A_2 values with the values of the control group.

Results

Figure 1 shows the mean mass concentrations of group I and group II phospholipases A_2, the mean catalytic activity concentration of phospholipase A_2 and the mean mass concentration of C-reactive protein at consecutive time points in sera of 12 panproctocolectomy patients. The mass concentration of group I phospholipase A_2 seemed to increase slightly (less than two-fold) from the first postoperative day on, peaked on the fourth postoperative day, and then decreased (fig. 1). The overall time-related change was not significant ($p = 0.100$, $F = 1.75$, $DF = 8$ and 78). The mass concentration of group II phospholipase A_2 was increased five-fold on the first postoperative day, and then decreased to almost preoperative levels during days two to five (fig. 1). The overall time-related change was significant at $p < 0.001$, $F = 3.79$, $DF = 8$ and 77. The difference between preoperative values and values on the first postoperative day was significant at $p < 0.001$, $F = 18.69$, $DF = 1$ and 77. The catalytic activity concentration of phospholipase A_2 was doubled on the first postoperative day, and then decreased (fig. 1). The overall time-related change was significant at $p = 0.030$, $F = 2.28$, $DF = 8$ and 77. The difference between preoperative values and values on the

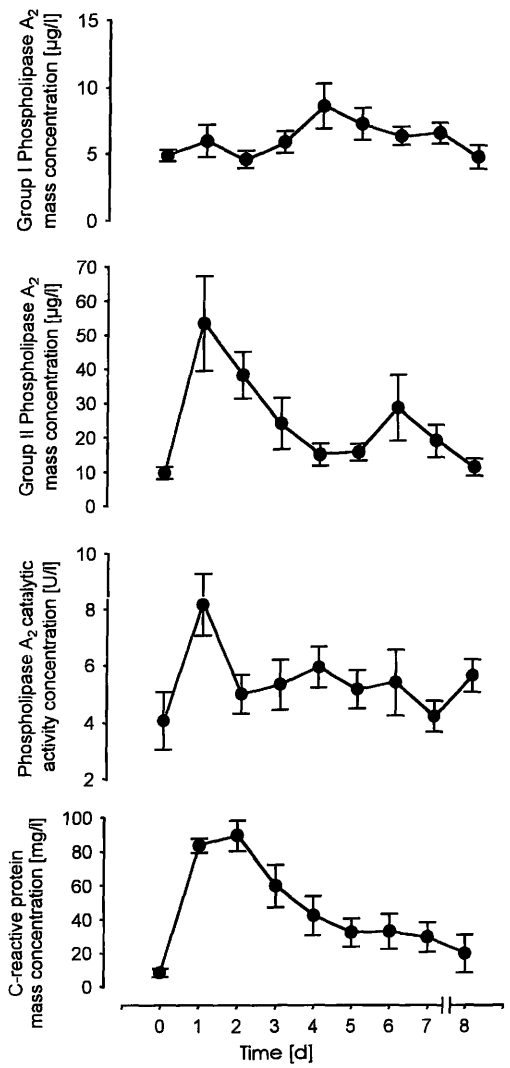

Fig. 1 Mass concentrations of group I phospholipase A_2 and group II phospholipase A_2, the catalytic activity concentration of phospholipase A_2 and the mass concentration of C-reactive protein in the sera of 12 consecutive patients undergoing a panproctocolectomy operation for ulcerative colitis (mean ±SEM). Preoperative samples (0) were taken in the morning before the panproctocolectomy operation, postoperative samples in the following mornings until the seventh postoperative day and at the follow up examination three months after the operation.

first postoperative day was significant at $p = 0.002$, $F = 10.65$, DF 1 and 77. The mass concentration of C-reactive protein reached the peak mean value on the second postoperative day and the pattern of the change of the mean values resembled that of the mean mass concentration of group II phospholipase A_2 (fig. 1). The overall time-related change of C-reactive protein was significant at $p < 0.001$, $F = 7.90$, DF 8 and 79. The difference between preoperative values and values on the second postoperative day was significant at $p < 0.001$, $F = 35.79$, DF 1 and 79.

The three patients with postoperative complications had peak values of group II phospholipase A_2 mass concentrations and phospholipase A_2 catalytic activity concentrations at the time of the respective postoperative complications (fig. 2). The episode of postoperative respiratory insufficiency was accompanied by the highest increases in group II phospholipase A_2 mass concentration, phospholipase A_2 catalytic activity concentration and C-reactive protein mass concentration (fig. 2).

The concentrations of all the quantities studied were at relatively low levels preoperatively and essentially similar levels were measured at the time of a check-up three months postoperatively. This was true for all patients including the three with early postoperative complications. Both preoperative and late postoperative (three months) levels of group II phospholipase A_2 (mean 9.7 µg/l and 12.7 µg/l, respectively) were moderately increased when compared with the level of a healthy control group (mean 5.5 µg/l). The differences were statistically significant ($T = 3.4$ and $T = 4.7$, respectively, $DF = 37$ and $p < 0.005$ for both comparisons).

Discussion

Experimental models have indicated that secretory phospholipases A_2 have diverse biological roles in host de-

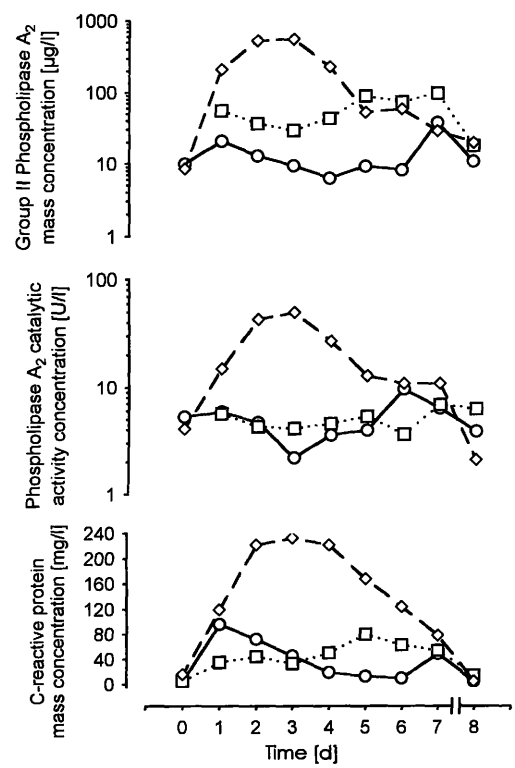

Fig. 2 Case profiles of group II phospholipase A_2 mass concentrations, the catalytic activity concentrations of phospholipase A_2 and the mass concentrations of C-reactive protein in three patients with postoperative complications after panproctocolectomy. The time points are the same as in figure 1. Note the logarithmic scale of phospholipase A_2 values. Patient A (–○–) was reoperated for intestinal obstruction on the seventh day after the panproctocolectomy operation. Patient B (···□···) had a pneumonia diagnosed by chest X-ray on the seventh postoperative day. Patient C (–◇–) had an episode of acute respiratory insufficiency and was therefore admitted to the intensive care unit on the third postoperative day.

fence, in the generation of lipid mediators and in the amplification of inflammatory reactions (12). Intravascular release and intravenous infusion of phospholipases A_2 are associated with systemic effects such as cardiovascular collapse and acute lung injury in experimental animals (20, 21). The mass concentration of group II phospholipase A_2 increases in serum in a similar way to that of other acute phase proteins in a variety of inflammatory diseases and postoperative states (22–24).

Various human cells and organs, including the small and large intestine, are capable of synthesising group II phospholipase A_2 (9, 25). Yet, it is not fully established which organ or cells are responsible for the secretion of the enzyme into the blood circulation. These (unknown) cells are of general interest since they might be indirectly responsible for the systemic organ effects of the enzyme. Earlier studies have shown that a major operation, even without an inflammatory disease, can elevate the mass concentration of group II phospholipase A_2 in serum (26–28). In the current study, the mass concentration of group II phospholipase A_2 and the catalytic activity concentration of phospholipase A_2 increased rapidly and temporarily and reached peak levels one day after the panproctocolectomy operation. The half-life of group II phospholipase A_2 in circulating human blood, in a situation where the synthesis of the enzyme is insignificant, is not known. Nevertheless, it is known from experiments with rats that the half-life of intravenously injected group I and group II phospholipase A_2 is 2.85 minutes and less than 30 seconds, respectively (29, 30). On the other hand, *Vadas* and co-authors reported that the estimated half-life of circulating soluble phospholipase A_2 in septic shock in man is 32 hours (31). The latter study was based on measurements from patients recovering from septic shock and probably represents a situation where the synthesis and the secretion of the enzyme into the circulation decrease slowly. This situation resembles the postoperative state of the present patients better than the experiments with intravenous injections of the enzyme preparations (29, 30). Based on the findings of the earlier animal experiments, we assume that the effect of possible intraoperative transfer of group II phospholipase A_2 from the large intestine into the blood circulation on the serum level of the enzyme is negligible. In the current study, we noted three cases with postoperative complications in which increases in the group II phospholipase A_2 levels in serum were observed later than in the group with no complications, and the peak levels corresponded to the time of the respective complication. Taking these facts together, we conclude that the rapid postoperative increase in the enzyme levels is attributable to significant postoperative secretion of group II phospholipase A_2 from some other organ than the removed large intestine. In an earlier study, hepatocytes were proposed as a major source of circulating group II phospholipase A_2 (32).

The results of the current work differ from those of earlier studies in one interesting detail. Peak values of group II phospholipase A_2 mass concentration were earlier found to occur typically on the second, third or fourth postoperative days (24, 26–28, 33), whereas we demonstrated peak values on the first postoperative day in patients with ulcerative colitis. This difference may be explained by the different study group in the current work in which all the patients had a chronic inflammatory disease and underwent major colonic surgery . The underlying inflammation may promote a faster response than in cases without preoperative inflammation. Furthermore, a surgical procedure on the colon may cause intraoperative translocation of endotoxin (34, 35), which is a potent inducer of phospholipase A_2 catalytic activity and group II phospholipase A_2 protein synthesis (36–38). The penetration of endotoxin through the intestinal wall is facilitated by mucosal inflammation (39, 40) which may also contribute to the proposed intraoperative translocation of endotoxin in this patient group. Earlier experimental studies have shown peak levels of phospholipase A_2 activity in the circulation 24 hours after controlled exposure to endotoxin in humans (37, 38). Another explanation for the rapid increase in group II phospholipase A_2 is the possible release of synthesised and stored enzyme due to chronic inflammation. Human neutrophils have been shown to release presynthesised group II phospholipase A_2 in response to stimulation (41). However, in a previous immunohistochemical study of the colonic wall and mesentery for group II phospholipase A_2 at the site of inflammation in ulcerative colitis, we could not detect any immunoreactivity in inflammatory cells, which were readily visualised in crypt abscesses and lymph nodes. Neither could we detect group II phospholipase A_2 mRNA in the inflammatory cells by in situ hybridisation (9). Taking these facts together, we assume that inflammatory cells are not the main source of circulating group II phospholipase A_2 in ulcerative colitis. The surgical trauma caused by a major abdominal operation most probably induces additional synthesis of group II phospholipase A_2 for systemic release in most patients, including those with ulcerative colitis. The observed lack of response on the second to fourth postoperative days in the current study may be explained by the corticosteroid therapy which was given to 11 of the 12 patients analysed. Corticosteroids inhibit the synthesis of group II phospholipase A_2 protein (36) and down-regulate the phospholipase A_2 enzyme activity (42, 43). The corticosteroid therapy may also explain why the postoperative increases in group II phospholipase A_2 mass concentrations were rather moderate (five-fold) in the current study compared with earlier studies (27, 28) in which the postoperative increases were more than ten-fold. The amplitude of increase in the mass concentration of group II phospholipase A_2 (five-fold) was greater than the increase of the catalytic activity

concentration of phospholipase A_2 (two-fold). This might be a result of the action of endogenous phospholipase A_2 inhibiting factors and (or) medication, which might inhibit phospholipase A_2 activity more than the synthesis of group II phospholipase A_2 protein. The increases observed in the mass concentration of group II phospholipase A_2 and the catalytic activity concentration of phospholipase A_2 in serum after panproctocolectomy are most probably normal host reactions to a major abdominal operation, and suggest a role for this enzyme in the generalised inflammatory reaction. On this basis, group II phospholipase A_2 can be considered as an acute phase protein.

The profile of the mean values of the catalytic activity concentration of phospholipase A_2 follows a pattern that could be a result of both group I phospholipase A_2 and group II phospholipase A_2 activity, because the profiles of the corresponding mass concentrations have peak values at the same time points as the catalytic activity concentration. However, the changes in the catalytic activity concentration on the fourth postoperative day and the overall time-related changes of group I phospholipase A_2 mass concentration were not significant ($p = 0.130$ and $p = 0.100$ respectively). Thus, the current data do not indicate a role for group I phospholipase A_2 in the postoperative recovery period in ulcerative colitis.

Comparisons between the preoperative enzyme levels and those at the follow-up three months later must be made with considerable caution because of the change in the medical treatment during that period. Especially the discontinuation of corticosteroid treatment may alter the result. We feel that reliable estimates of the late impact of panproctocolectomy on phospholipase A_2 enzyme levels cannot be based on the results of the current study. Nevertheless, we have shown that the removal of the large intestine does not terminate the secretion of group II phospholipase A_2 into the circulation in patients with ulcerative colitis. We have also shown that these patients have increased levels of group II phospholipase A_2 in serum preoperatively and postoperatively when compared with a control group of healthy blood donors.

Conclusion

The catalytic activity concentration of phospholipase A_2 and the mass concentration of group II phospholipase A_2 increase rapidly and temporarily after panproctocolectomy in sera of patients with ulcerative colitis. The observation supports the idea that group II phospholipase A_2 is an acute phase protein and indicates that the large intestine is not the main source of circulating group II phospholipase A_2 in patients with active ulcerative colitis. The results also support the assumption that the catalytic activity of phospholipase A_2 in serum is attributable to group II phospholipase A_2.

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Corresponding author: Dr. Markku Haapamäki, Department of Surgery, University of Turku, Kiinamyllynkatu 4–8, FIN-20520 Turku, Finland
Tel.: +358-2-2611611, Fax: +358-2-2612284,
e-mail markku.haapamaki@utu.fi