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Increased Biosynthesis of Vasoactive Prostanoids in Schönlein-Henoch Purpura

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ABSTRACT. Schönlein-Henoch purpura (SHP) is an acute immune-mediated vasculitis characterized by infiltration of polymorphonuclear leukocytes into the vessel wall causing damage to the vascular endothelium by the release of proteolytic enzymes. The local inflammatory and thrombotic process may be regulated by increased biosynthesis of vasoactive prostanoids. We investigated the biosynthesis of thromboxane A_2 (TxA_2), a potent vasoconstrictor and platelet agonist, prostacyclin (PGI_2), a vasodilator and platelet antagonist, and prostaglandin E_2, a mediator of inflammation, in 14 children with SHP by physicochemical analysis of index metabolites in plasma and urine. TxA_2 and PGI_2 biosynthesis in the systemic circulation was significantly elevated in the acute phase of the disease and correlated with the degree of clinical symptoms. Recurrent episodes of the disease were associated with phasic increases of plasma and urinary TxA_2 and PGI_2 metabolites. Renal TxA_2 formation was highest in two patients presenting with the nephrotic syndrome and extracapillary glomerulonephritis. Prostaglandin E_2 biosynthesis in the systemic circulation was increased in the acute phase of the disease. The enhanced TxA_2 formation is consistent with phasic platelet activation in SHP. The increased PGI_2 biosynthesis reflects endothelial cell damage and may be a response of vascular endothelium to modulate platelet-vessel wall and leukocyte-vessel wall interactions. Increased prostaglandin E_2 formation, which probably derives from activated polymorphonuclear leukocytes and macrophages, is thought to be related to the inflammatory process in SHP. (*Pediatr Res* 32: 137–140, 1992)

Abbreviations

SHP, Schönlein-Henoch purpura
PGE_2, prostaglandin E_2
PGE-M, 7 α-hydroxy-5,11-diketo-tetranor-prostane-11, 16-dioic acid
PGI_2, prostacyclin
TxA_2, thromboxane A_2
TxB_2, thromboxane B_2
2,3-dinor-TxB_2, 2,3-dinor-thromboxane B_2
11-dehydro-TxB_2, 11-dehydro-thromboxane B_2
6-keto-PGF_{1a}, 6-keto-prostaglandin $F_{1\alpha}$
2,3 dinor-6-keto-PGF_{1a}, 2,3-dinor-6-keto-prostaglandin $F_{1\alpha}$

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SHP is the most common form of vasculitis in children (1). The vasculitis is initiated by the subendothelial deposition of IgA/IgG immune complexes in small blood vessels (2). Complement activation induces infiltration of polymorphonuclear leukocytes, which by the release of proteolytic enzymes cause damage to the vessel wall with secondary thrombosis and hemorrhage (3). The altered integrity of the vascular endothelium is likely to involve changes in prostanoid biosynthesis at the platelet vascular interface. TxA_2, the major cyclooxygenase product of arachidonic acid in platelets, is a potent platelet aggregator and vasoconstrictor (4). The potential pathophysiologic role of TxA_2 in acute immune-mediated vasculitic disorders has not yet been elucidated.

In the present study, we investigated TxA_2 biosynthesis in children with SHP prospectively during the disease process. To avoid sampling and analytical problems, TxA_2 biosynthesis was examined by a highly specific and sensitive method, which measures two major urinary enzymatic metabolites, 11-dehydro-TxB_2 and 2,3-dinor-TxB_2, which are index metabolites of TxA_2 activation in the systemic circulation (5, 6), and by measuring urinary TxB_2, which predominantly reflects renal TxA_2 formation (7). In addition, circulating TxA_2 levels were estimated by determination of plasma 11-dehydro-TxB_2, the most abundant enzymatic metabolite of TxB_2 (6, 8).

Another prostanoid that may modulate the function of the altered endothelium in SHP is PGI_2, the major cyclooxygenase product of arachidonic acid in vascular endothelium, with potent vasodilative and antiaggregatory properties (9). PGI_2 biosynthesis was assessed by use of a highly specific, noninvasive method. This is the measurement of its urinary metabolite 2,3-dinor-6-keto-PGF_{1a} as an index of systemic PGI_2 formation (10) and measurement of 6-keto-PGF_{1a}, which is derived predominantly from the kidney (7). In parallel, the biosynthesis of PGE_2, a putative mediator of inflammation with vasodilative and permeability increasing properties (11), was examined by measuring its urinary metabolite, PGE-M, as an index metabolite of systemic PGE_2 activity (12).

MATERIALS AND METHODS

Patients and study design. Fourteen children (four girls and 10 boys), aged 2.5 to 16 (median 6) y, were studied. All had the typical cutaneous manifestations of SHP and joint symptoms; eight patients had gastrointestinal involvement and seven patients had renal involvement with microhematuria and proteinuria. Two patients developed the nephrotic syndrome with impaired renal function. In the latter two patients, renal biopsy showed diffuse extracapillary glomerulonephritis with 100% cellular crescents and endo/extracapillary glomerulonephritis with 100% cellular crescents, respectively. By immunofluorescence, both biopsies contained granular deposits of IgA in the glomerular mesangium.

Patients who had taken aspirin or other cyclooxygenase inhib-

itors in the preceding 10 d were excluded. Patients were prospectively assessed by their attending physicians according to a clinical score (Table 1) to quantitate the severity of their extrarenal organ involvement. Patients with a clinical score > 2 (algebraic sum of the three organ involvements) were assigned to the acute phase; the recovery phase was defined as the absence of any extrarenal symptoms of SHP (clinical score = 0).

On admission, blood was obtained for determination of plasma 11-dehydro-TxB_2. Subsequent blood samples were taken serially every 3rd day. Simultaneously, urine was collected during 24 h from admission until discharge from the hospital. Total urine output was determined and aliquots were stored at −80°C for analysis of prostanoids. To examine the association between clinical activity and prostanoid activity, the severity of clinical involvement was quantified by a score related to skin, joint, and intestinal manifestations (Table 1). The plasma and urine samples obtained in the presence of most severe clinical symptoms (*i.e.* with the highest algebraic sum of the three extrarenal organ involvements) were compared with those obtained in the recovery phase and with controls (12 age- and sex-matched healthy children). Informed consent was obtained from each child's parent(s) before entry into the study. The protocol was approved by the Ethics Committee of the University of Heidelberg.

Analytical methods. For the analysis of urinary and plasma prostanoids, gas chromatographic mass spectrometric methods were used, which have been described previously (13). Following the principle of stable isotope assays, endogenous prostanoids were quantitated against their respective deuterated analogues, which were added as internal standards at the beginning of the procedure. The determination of 6-keto-PGF_{1a} involved extraction by octadecyl silica and normal phase silica cartridges, purification by HPLC, derivatization to the methylester-methoxime-trimethylsilylethers, and quantitation by capillary gas chromatography mass spectrometry in the electron impact mode (13). The 2,3-dinor-6-keto-PGF_{1a} was purified by extraction and back extraction under alkaline and acidic conditions and thin-layer chromatography. The pentafluorobenzylester-methoxime-trimethylsilyether derivative was analyzed by gas chromatography mass spectrometry in the negative ion chemical ionization mode (13). The 2,3-dinor-TxB_2 and TxB_2 were extracted chemoselectively by phenylboronic acid columns, purified by thin-layer chromatography, derivatized, and quantitated in analogy to 2,3-dinor-6-keto-PGF_{1a} (13). The 11-dehydro-TxB_2 was extracted from plasma and urine by octadecyl silica cartridges, purified by thin-layer chromatography, and analyzed as the pentafluorobenzylester-trimethylsilylether by gas chromatography-tandem mass spectrometry as described previously (6). PGE-M was extracted as the methoxime by ethyl acetate/hexane, derivated to the pentafluorobenzylester, purified by thin-layer chromatography, the trimethylsilylether was formed, and PGE-M was quantified by gas chromatography-tandem mass spectrometry. Analyses of creatinine in serum and urine were performed by routine laboratory methods.

Prostanoid excretion rates were expressed as ng/h/1.73 m^2 calculated per 100 mL glomerular filtration rate (creatinine clearance) to correct for the influence of different degrees of glomerular function on prostanoid excretion. A previous report had established a close positive correlation between prostanoid excretion and glomerular filtration rate in chronic renal failure (14).

Table 1. *Clinical scores to assess degree of extrarenal organ involvement during acute phase of SHP*

Organ	Degree of severity
Skin	0 = no symptoms
	1 = sporadic petechiae
	2 = widespread purpura
Joints	0 = no symptoms
	1 = arthralgia in a single joint
	2 = arthralgia in several joints
Gastrointestinal tract	0 = no symptoms
	1 = abdominal pain with occult melaena
	2 = hemorrhagic colitis

Significant differences between the data were evaluated by the Wilcoxon signed rank-test for paired data or by the Mann-Whitney test where appropriate. $p < 0.05$ was accepted as being statistically significant. Associations between variables were investigated by linear regression analysis.

RESULTS

Plasma levels of 11-dehydro-TxB_2 and peak urinary excretion rates of 11-dehydro-TxB_2 and 2,3-dinor-TxB_2 were significantly elevated in the acute phase of SHP compared to the recovery phase and to the control group (Table 2). Excretion of 11-dehydro-TxB_2 was almost twice that of 2,3-dinor-TxB_2 in the acute phase and dropped in parallel in the recovery phase to reach similar values as in controls. Urinary 11-dehydro-TxB_2 and 2,3-dinor-TxB_2 excretion were correlated ($r = 0.57$; $p < 0.001$). TxB_2 excretion was increased in the acute phase, but in contrast to the index metabolites of systemic Tx activity it did not significantly differ between acute and recovery phase (Table 2). However, there was a persistently high TxB_2 excretion in the recovery phase of the two patients with nephrotic syndrome and histologically proven glomerulonephritis (20.9 and 28.5 ng/h/1.73 m^2) compared to that of the other 12 patients (median 10.2; range 4.9–19.8 ng/h/1.73 m^2).

Concomitant with the enhanced systemic TxA_2 formation, PGI_2 biosynthesis was increased in the acute phase as assessed by the urinary excretion rate of 2,3-dinor-6-keto-PGF_{1a} (Table 2). This was significantly correlated with 11-dehydro-TxB_2 ($r = 0.72$; $p < 0.001$) and 2,3-dinor-TxB_2 ($r = 0.56$; $p < 0.005$) in the acute phase. In contrast, urinary excretion of 6-keto-PGF_{1a} in the acute phase did not differ significantly from that in the recovery phase and from controls. A significant correlation was found between the algebraic sum of the clinical scores and plasma 11-dehydro-TxB_2 ($r = 0.54$; $p < 0.01$), urinary 11-dehydro-TxB_2 ($r = 0.69$; $p < 0.0001$) (Fig. 1), urinary 2,3-dinor-TxB_2 ($r = 0.62$; $p < 0.001$), and 2,3-dinor-6-keto-PGF_{1a} ($r = 0.64$; $p < 0.0005$). PGE-M excretion rates in the acute phase were significantly higher ($p < 0.01$) than during recovery (Table 2).

DISCUSSION

This study demonstrates increased systemic TxA_2 formation in the acute phase of patients with SHP that normalizes during recovery from the disease. TxA_2 biosynthesis was assessed by specific measurement of indexes of the two major pathways of TxA_2 metabolism in the systemic circulation, 11-dehydro-TxB_2 and 2,3-dinor-TxB_2 (15, 16).

The measurement of urinary metabolites has the advantage of being noninvasive and representing time-integrated indexes of TxA_2 biosynthesis (17). As in healthy controls (6) and in conditions with increased platelet-vessel wall interaction (14, 15), the endogenous urinary 11-dehydro-TxB_2 excretion rates exceeded those of endogenous urinary 2,3-dinor-TxB_2 in the patients with SHP indicating that 11-dehydro-TxB_2 is the more abundant urinary TxA_2 metabolite. The combined analysis of both the 2,3-dinor and the 11-dehydro metabolites permits us to rule out that increased excretion of one metabolite reflects just a shift in the metabolic disposition of TxA_2 and not a true increased TxA_2 biosynthesis. The high plasma concentration of the major enzymatic metabolite of TxA_2, 11-dehydro-TxB_2, in the acute phase supports our hypothesis of an exaggerated TxA_2 synthesis in SHP.

Because thrombocytes are the major source of TxA_2 in humans (4), the increased TxA_2 formation can be attributed primarily to platelet activation. Vascular endothelium and macrophages may contribute to a small extent to enhanced TxA_2 formation. In an

Table 2. *Plasma 11-dehydro-TxB_2 and urinary excretion rates of 11-dehydro-TxB_2, 2,3-dinor-TxB_2, TxB_2, 2,3-dinor-6-keto-PGF_{1a}, 6-keto-PGF_{1a}, and PGE-M in 12 healthy controls and in 14 patients with SHP during acute and recovery phase of disease**

Variable	Controls (ng/h/1.73 m^2)	SHP	
		Acute phase (ng/h/1.73 m^2)	Recovery phase (ng/h/1.73 m^2)
Plasma 11-dehydro-TxB_2	8.3 (2.4–12.3)	29.8†‡ (2.0–95.7)	9.5 (1.7–17.6)
Urinary 11-dehydro-TxB_2	30.7 (3.5–65.1)	113.9§‖ (14.6–547.3)	22.1 (0.8–39.3)
Urinary 2,3-dinor-TxB_2	14.4 (6.2–37.6)	60.9§‖ (15.3–338.2)	16.2 (6.7–30.7)
Urinary TxB_2	2.3 (0.8–10.1)	12.6‡ (3.0–106.1)	13.3¶ (3.5–28.5)
Urinary 2,3-dinor-6-keto-PGF_{1a}	7.4 (3.9–10.1)	17.6‖** (6.0–58.4)	7.3 (3.6–14.9)
Urinary 6-keto-PGF_{1a}	4.5 (1.0–13.2)	6.2 (1.0–79.8)	3.1 (1.8–7.4)
PGE-M	219 (72–484)	586**†† (150–2842)	204 (79–388)

* Prostanoid excretion rates were standardized for 100 mL glomerular filtration rate. Values are given as median and range.
† $p < 0.05$, acute phase *vs* recovery.
‡ $p < 0.05$, acute phase *vs* controls.
§ $p < 0.005$, acute phase *vs* recovery.
‖ $p < 0.001$, acute phase *vs* controls.
¶ $p < 0.05$, recovery *vs* controls.
** $p < 0.01$, acute phase *vs* recovery.
†† $p < 0.005$, acute phase *vs* controls.

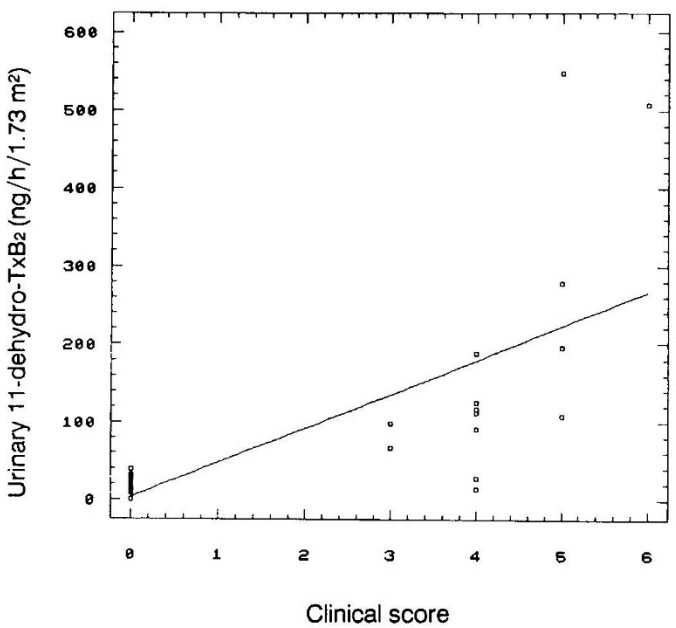

Fig. 1. Correlation of urinary 11-dehydro-TxB_2 with the highest algebraic sum of the clinical scores in 14 children with SHP during the acute phase of the disease and recovery ($r = 0.69$; $p < 0.0001$).

animal model of immune complex vasculitis, platelet accumulation was demonstrated at skin sites in reversed passive Arthus reactions (18), supporting the concept that increased TxA_2 formation reflects platelet activation in SHP representing a model of immune complex vasculitis in humans. The close temporal relation between clinical activity and systemic TxA_2 formation (Fig. 1) indicates phasic platelet activation during episodes of active disease. Other methods to investigate platelet function, such as measurement of β-thromboglobulin and platelet factor 4, were not obtained in this study because of technical factors stimulating platelet activation artifactually during blood sampling, especially in young children.

Renal TxB_2 formation was investigated in our study by measuring the urinary excretion rates of the TxA_2 hydration product TxB_2. This predominantly reflects renal TxA_2 activity when concomitant extrarenal TxA_2 stimulation is excluded (7). It is of interest that renal TxA_2 excretion was higher in two patients with glomerulonephritis and nephrotic syndrome compared to the other cases. It is noteworthy that patients with lupus nephritis, another form of renal vasculitis, present increased urinary TxB_2 excretion, which correlates with the degree of glomerular injury (19). Pharmacologic intervention with a selective TxA_2 antagonist significantly improved renal function in this situation (20). Accordingly, the investigation of renal TxA_2 formation in patients with SHP nephritis should be pursued.

In addition to an increased TxA_2 formation, the present study demonstrates enhanced PGI_2 formation in patients with SHP. This prostanoid is the principal metabolite of arachidonic acid produced by vascular endothelium and has potent vasodilator and platelet antiaggregatory effects (9). Under physiologic conditions, its circulating blood concentration is too low to exert a biologic effect, but platelet-inhibitory concentrations are formed at the site of vessel injury to limit the degree of platelet activation (21). Because PGI_2 formation in our patients was positively correlated to TxA_2 formation, it is possible that increased endothelial PGI_2 biosynthesis is a response of vascular endothelium to compensate for TxA_2-mediated platelet activation and does not merely reflect damage to the endothelium. Endothelial cell PGI_2 is also thought to influence leukocyte/vessel wall interactions by blocking leukocyte adhesion after stimulation (22). It has been demonstrated that PGI_2 synthesis in vascular cells can be induced by platelet activating factor (23) and IL-1 (24), which are both stimulated in immune-mediated vascular disorders (25, 26). Thus, increased PGI_2 formation in SHP may not only regulate local thrombotic events but also modulate the inflammatory processes.

A previous study has reported decreased PGI_2 stimulating activity *ex vivo* in children with SHP (27). In contrast, the present study demonstrates that the *in vivo* PGI_2 biosynthesis is increased in the acute phase of SHP. A similar discrepancy between *in vivo* and *ex vivo* PGI_2 production has also been observed in hemolytic-uremic syndrome (14) and may be explained by the fact that

measurement of *ex vivo* PGI_2 stimulating activity, in contrast to PGI_2-metabolite excretion rates, does not reflect the actual biologically effective activity of PGI_2 *in vivo*.

The elevated systemic PGE_2 production found in our study, which probably derives from activated polymorphonuclear leukocytes and macrophages, may be related to the inflammatory process observed in SHP. PGE_2 is known to be a mediator of inflammation by promoting blood flow in the inflamed region and thus enhancing edema formation and leukocyte infiltration (28). On the other hand, PGE_2 has a local immunosuppressive effect by inhibiting lymphocyte transformation due to mitogen stimulation, antibody production, and lymphokine production. Therefore, it is difficult to assess whether local PGE_2 production enhances or suppresses the inflammatory process in SHP.

In conclusion, this study demonstrates increased TxA_2 and PGI_2 biosynthesis in children with SHP as a model of immune-mediated vasculitis consistent with increased platelet-vessel wall and leukocyte-vessel wall interaction in the disease process. Increased TxA_2 and PGI_2 formation have been reported in other diseases with increased platelet vessel wall interaction such as severe atherosclerosis (15), unstable coronary heart disease (29), and systemic sclerosis with Raynaud's phenomenon (30) as models of chronic degenerative vasculopathy and in hemolytic-uremic syndrome (14) as a model of acute toxic vasculopathy. The similarity of these findings suggests that although damage to the vascular endothelium may result from a variety of insults the response of the vascular endothelium is rather uniform.

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