Reviews

European Journal of
Pediatrics

Eur J Pediatr (1988) 147:341–349

The role of eicosanoids in paediatrics

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Abstract. Prostanoids are unsaturated cyclic fatty acids, are synthesized primarily from arachidonic acid, and, like the leukotrienes, belong to the growing family of eicosanoids. As tissue hormones, prostanoids act on specific receptors near their site of synthesis and degradation. Prostanoids operate as modulators and mediators in a large spectrum of physiological processes. They are involved in the regulation of maternal and fetal circulation, patency of the ductus arteriosus, platelet-vessel wall interaction and kidney function. Besides their physiological function in protecting organ perfusion under stress conditions, they are also involved in diseases as described in the hyperprostaglandin E_2-syndrome or – together with leukotrienes-in inflammatory processes. More specific pharmacological tools than the nonsteroidal antiinflammatory drugs, such as receptor antagonists, selective synthesis inhibitors, and eicosanoid analogues offer the prospect of enriching our arsenal of pharmacotherapeutic interventions in a variety of diseases. Before active intervention, however, more and specific biochemical analyses are required to identify the pathophysiological role of eicosanoid.

Key words: Eiosanoids – Prostaglandins – Modulation – Mediation – Early life

Introduction

The aims of this review are (a) to focus on the principal role of eicosanoids as modulators and mediators in physiological and pathophysiological processes in general, (b) to discuss some essential analytical aspects, and (c) to demonstrate how this knowledge has already influenced our understanding and management of a variety of clinical conditions, with particular emphasis on paediatrics. Finally, future aspects of eicosanoid research, a rapidly expanding field in experimental medicine, are briefly considered.

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Abbreviations: PG = prostaglandin; Tx = thromboxane; PGE-M = 7α-hydroxy-5,11-diketotetranorprostane-1,16-dioic acid; SRS-A = slow reacting substance of anaphylaxis; NSAI drugs = nonsteroidal anti-inflammatory drugs; PDA = patent ductus arteriosus

History

The history of eicosanoid research is an excellent example of exponential growth in a new scientific area. Prostaglandins were discovered as active compounds in the late 1920s by Kurzrock and Lieb, who found that human semen could cause strips of uterine smooth muscle to contract [54]. These observations were extended by Goldblatt [34], who also discovered that human semen reduced blood pressure when injected intravenously into animals. It was von Euler [19], who provisionally coined the term "prostaglandin" in 1935, because he felt that the major source of these active substances was probably the prostate gland.

Twenty-five years later, Bergström and Sjövall [5] isolated the first two classical prostaglandins, PGE and PGF. Subsequently, their structures were elucidated by Bergström and his group [6] using gas chromatography-mass spectrometry. In 1964, the groups of van Drop and Bergström independently achieved the biosynthesis of prostaglandin (PG) E_2 from arachidonic acid [7, 17]. A variety of other oxidative metabolites of arachidonic acid have been discovered since. In 1975, Hamberg et al. [42] described the thromboxanes, potent proaggregatory and vasoconstrictor compounds. Two years later, the vasodilator PGI_2 was discovered in the vascular endothelium [71]. Leukotrienes were defined as the active principle of the slow reacting substance of anaphylaxis (SRS-A) by Samuelsson's group in 1979 [43]. The link with clinical medicine

Table 1. Taxonomy of primary eicosanoids

I. Prostanoids = cyclooxygenase products	
1. Prostaglandins	PGE_1, PGE_2, PGE_3
	$PGF_{2\alpha}$, $PGF_{3\alpha}$
	PGD_2
	PGI_2, PGI_3 = prostacyclines
2. Thromboxanes	TxA_2, TxB_2, TxA_3
II. Lipoxygenase products	
1. Leukotrienes	LTA_4
	LTB_4, LTB_5
	LTC_4, LTD_4, LTE_4, LTF_4
2. Hydroxyeicosatetraenoic acids (HETE)	5-HETE, 12-HETE, 15-HETE
3. Lipoxins	Lipoxin A, Lipoxin B

was established in 1971 when Vane [115] discovered that non-steroidal anti-inflammatory (NSAI) drugs inhibited PG synthesis. All 20-carbon derivatives of unsaturated fatty acids, predominantly arachidonic acid, are now called eicosanoids. The taxonomy of these compounds is shown in Table 1.

Biosynthesis and metabolism

Eicosanoids are not stored in any tissue. Upon various stimuli they are generated by de novo synthesis and are quickly inactivated due to chemical instability or by metabolizing enzymes. These compounds are therefore considered as local hormones without significant systemic effects via the circulation. Eicosanoids can be synthesized principally from three different fatty acids: (a) dihomo-gamma-linolenic acid with three double bonds (C20:3ω6), the precursor of the monoenoic prostanoids, e.g. PGE_1; (b) arachidonic acid, which is the predominant substrate of endogenous eicosanoid synthesis, an essential fatty acid with four double bonds (C20:4ω6), and the precursor of the dienoic prostanoids, e.g. PGE_2; and finally (c) eicosapentaenoic acid (C20:5ω6), a fatty acid with five double bonds, the major substrate of eicosanoid synthesis in marine animals, and the precursor of the trienoic prostanoids, e.g. PGE_3, PGI_3 and TxA_3 and the leukotrienes with five double bonds, e.g. LTB_5. Eicosapentaenoic acid has attracted particular interest recently, because it has the potential to shift the balance between eicosanoids. Diets rich in eicosapentaenoic acid, e.g. fish oil, might have a favourable impact on such diverse disease processes as atherosclerosis [50, 118] or chronic inflammation [58, 112].

These precursor fatty acids, predominantly arachidonic acid, are esterified in the 2-position of cellular phospholipids and do not exist as free acids to a significant extent. Thus the generation of free arachidonic acid from phospholipids is the rate-limiting step for the formation of biologically active eicosanoids. The liberation of arachidonic acid occurs through stimulation of specific cell surface receptors, the subsequent activation of a complex messenger system, and phospholipases C and A_2 [55, 83]. Arachidonic acid is released in response to various stimuli such as angiotensin II, vasopressin, adrenalin, thrombin, collagen, ADP, histamine, bradykinin, platelet activating factor, mechanical stimulation, and hyperosmolality, depending on the cells involved. Apparently the small pool of free arachidonate is modulated by the rates of liberation and reacylation into phospholipids [51]. Moreover, glucocorticoid-induced inhibitors of phospholipase activity, like lipocortin, are able to suppress the activity of the arachidonate cascade, as demonstrated in vitro [25].

Once released, arachidonic acid is metabolized to oxidative products by at least two distinct enzymatic pathways, cyclooxygenase and lipoxygenase (Fig. 1) [73]. Cyclooxygenase converts arachidonic acid to PGG_2 and PGH_2, which are unstable endoperoxide intermediates in the formation of prostanoids. This enzyme is inhibited by aspirin and all the other non-steroidal anti-inflammatory drugs by different mechanisms [26]. The endoperoxides are then enzymatically converted to the prostanoids. The primary prostaglandins are inactivated by specific enzymes that are widely distributed in the body, particulary in the lung, giving rise to as many as 20 metabolites for individual prostanoids [87]. After oxidation of the 15-hydroxy group and reduction of the double bond between C13 and C14, the side chains of the prostanoic acid are

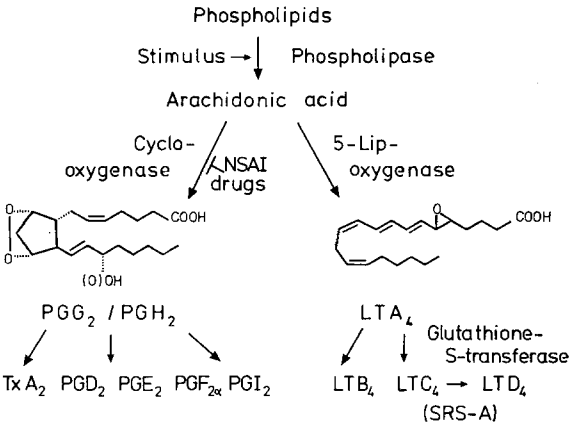


Fig. 1. Simplified scheme of the arachidonate cascade leading to the generation of prostanoids via the cyclooxygenase and to leukotrienes via the 5-lipoxygenase

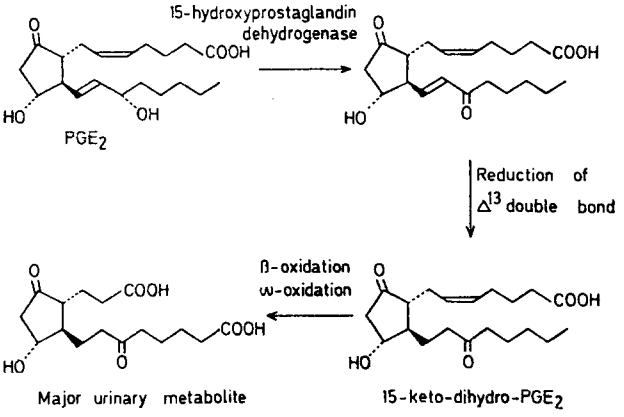


Fig. 2. Metabolic pathway of the primary prostaglandin E_2 leading to the formation of the major urinary metabolite of the E-prostaglandins (PGE-M)

subjected to β- and ω-oxidation, leading to more polar metabolites which are excreted into the urine (Fig. 2). These so-called index metabolites are 7α-hydroxy-5,11-diketotetranorprostane-1,16-dioic acid (PGE-M) and 5α,7α-dihydroxy-11-ketotetranorprostane-1,16-dioic acid (PGF-M) for PGE_2 and $PGF_2\alpha$, respectively [93]. PGD_2 is, to a significant degree, converted to $PGF_2\alpha$ isomers [64]. Metabolic pathways similar to those for PGE_2 and $PGF_2\alpha$ have been described for TxA_2 [57, 87] and PGI_2 [9], although these highly unstable prostanoids primarily break down non-enzymatically to TxB_2 and 6-keto-$PGF_1\alpha$, respectively. Major urinary metabolites of TxB_2 are 2,3-dinor-TxB_2 and 11-dehydro-TxB_2 [87, 99], while PGI_2 and 6-keto-$PGF_1\alpha$ are further metabolized and excreted into the urine as 2,3-dinor-6-keto-$PGF_1\alpha$ and 2,3-dinor-6,15-diketo-$PGF_1\alpha$ [9].

The lipoxygenase reactions, which are not affected by non-steroidal anti-inflammatory drugs, lead to the formation of leukotrienes and some other non-cyclized hydroxy fatty acids (Fig. 1) [73, 111]. Leukotriene A_4 (LTA_4) is a 5,6-epoxide of arachidonate, which can either be converted to LTB_4 by enzymatic stereospecific hydration or to LTC_4 by addition of glutathione, giving rise to the peptido-leukotriene series. The removal of glutamate from LTC_4 by γ-glutamyl transpeptidase yields LTD_4, which is further metabolized to LTE_4 by cleav-

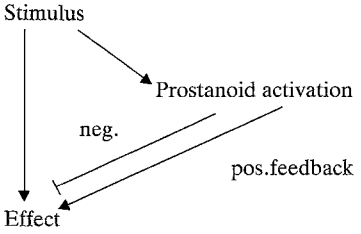
Table 2. Platelet and smooth muscle activity of prostanoids

	Platelet aggregation	Aorta	Peripheral artery	Umbilical artery	Ductus arteriosus	Renal artery	Pulmonary artery	Cerebral artery	Bronchial muscle
PGG_2	↑	↑	↑	↑	↓	↓	↑	↓	↑
PGH_2	↑	↑	↑	↑	↓	↓	↑	↓	↑
TxA_2	↑	↑	↑	↑	↑–	↑	↑	↑–	↑
PGD_2	↓	–	↑–		↓	↑	↓↑	↓	↑
PGE_2	↑↓		↓	↑	↓	↓	↓	↓	↓
$PGF_{2\alpha}$	–		↑	↑	–	–	↑	↑	↑
PGI_2	↓	↓	↓	↓	↓	↓	↓	↓	–

↓ = relaxation desaggregation; ↑ = constriction aggregation; – = no effect

Table 3. Biological profile of leukotrienes

LTB_4	LTC_4/LTD_4 (SRS-A)
– Chemotaxis	– Pulmonary vasoconstriction
– Adhesion and aggregation of neutrophiles	– Bronchial constriction
– Degranulation	– Plasma exudation
– Plasma exudation	– Mucus secretion
– Activation of phospholipases (prostanoid release)	– Activation of phospholipases (prostanoid release)



Stimulus	Effect	Negative (attenuation) Prostanoid
Catecholamines	Lipolysis	PGE_2
ADH	Water retention	PGE_2
Angiotensin II	Vasoconstriction	PGE_2
Sympathetic nerve stimulation	Norepinephrine release	PGE_2
Platelet adhesion	Platelet aggregation	PGI_2
Interleukin I release during macrophage phagocytosis	T-Cell proliferation	PGE_2
Stimulus	**Effect**	**Positive (potentiation) Prostanoid**
Bradykinin	Algesia	PGE_2
Peptido-LT's	Pulmonary vasoconstriction	TxA_2

Fig. 3. Principle mechanism of prostanoid modulation with some examples of negative *(neg.)* and positive *(pos.)* feed-backs

age of glycine. At present, only a few metabolites of leukotrienes have been identified, such as 20-hydroxy- and 20-carboxy-LTB_4 [43, 100] and N-acetyl-LTE_4 [40]. Besides the 5-lipoxygenase pathway, 12- and 15-lipoxygenases have been characterized, the significance of which in vivo remains to be determined. The same applies to the lipoxines, trihydroxy derivatives of arachidonic acid with a possible inhibitory effect on natural killer cells [101].

Receptors and effects

The various biological functions of prostanoids and leukotrienes are listed in Tables 2 and 3. The specific and selective effects of prostanoids on cell function have led to the conclusion that multiple receptors exist. PGE_2 and PGI_2 are potent vasodilators and act by stimulation of adenylate cyclase. Although no specific receptor antagonists are available, it is currently assumed that there are at least two, perhaps three, receptors for vasodilatory prostanoids (PGI_2, PGE_2 and PGD_2) [2]. PGI_2 and PGD_2 exert their platelet desaggregating activity via separate receptors [68]. TxA_2 induces vasoconstriction and platelet aggregation through a receptor that is shared by the endoperoxides PGG_2 and PGH_2 [41]. Specific TxA_2-receptor antagonists have been discovered which may have a potential as vasodilatory and anti-aggregatory agents for clinical use [39, 76].

Some progress has been made in developing antagonists for the peptidoleukotrienes LTC_4 and LTD_4 [67, 73, 111]. Respiratory, vascular, and intestinal smooth muscle contractions can be antagonized by compounds from the FPL series, early and relatively unselective antagonists. More specific compounds are currently under investigation [24]. In general LTE_4 is less potent than LTC_4 and LTD_4, also with respect to plasma exudation and mucus secretion. LTB_4 is a potent chemotactive agent for neutrophils. Its binding sites are distinct from those for peptidoleukotrienes [62].

Principles of the mechanism of action of eicosanoids

Eicosanoids are considered as local hormones. Their mechanisms of action are more complex than those of classical hormones, which are synthesized in and released from a specific organ or organ system remote from the target organs and transported by the circulation. At the target organ, classical hormones have a clear-cut, unidirectional effect. Prostanoids are part of a complex regulatory system. They have either modulator or mediator function (Fig. 3, 4). In contrast to classical hormonal systems almost all nucleated cells are capable of releasing prostanoids. This biosynthetic capacity is not restricted to a specialized organ or tissue, although some pros-

Stimulus
↓
Prostanoid-activation
↓
Effect

Stimulus	Prostanoid	Effect
Interleukin I	PGE_2	Fever
Endotoxin	TXA_2	Pulmonary hypertension
Collagen	PGH_2, TXA_2	Platelet aggregation
Artificial ventilation	PGE_2, PGI_2	Persistent ductus arteriosus
Malignancy	PGE_2	Osteolysis, hypercalcaemia
Storage diseases in the kidney	PGE_2	Renal water and electrolyte wastage
Bradykinin	PGE_2, PGI_2	Vasodilatation
Furosemide	PGE_2, PGI_2	Renin release

Fig. 4. Principle mechanism of prostanoid-induced mediation with some examples

tanoids are predominantly produced by certain cell types. Thus, platelets have a huge capacity for the production of thromboxane A_2, while PGI_2 is the major cyclooxygenase product released by endothelial cells. Basophils and mast cells primarily synthesize the peptidoleukotrienes and PGD_2.

The modulator function (Fig. 3) can easily be demonstrated by the negative feedback mechanism of PGE_2 during catecholamine – induced lypolysis. In parallel with the release of fatty acids PGE_2, a potent inhibitor of catecholamine-induced lipolysis [28], is synthesized. Similar negative feedback mechanisms exist in the kidney, e.g. the ADH antagonism of renal PGE_2 which is stimulated by the renal effects of ADH [95]. Another example is the simultaneous release of interleukin I and PGE_2 from macrophages during phagocytosis. While interleukin I stimulates, PGE_2 inhibits lymphocyte proliferation [36].

Prostanoids can also operate as mediators (Fig. 4). Interleukin I induces fever by stimulating hypothalamic PGE_2 synthesis, which changes the set-point of body temperature [14]. Even within the arachidonate cascade, opposing mediators are released. The cyclooxygenase product PGI_2 causes vasodilation and inhibits platelet aggregation, whereas TxA_2 is a potent vasoconstrictor and platelet aggregator [42, 70]. Thus, unspecific pharmacological intervention by inhibition of cyclooxygenase activity in a variety of tissues or by feeding arachidonate [103] may not change the balance between antagonists, and no net effects will be observed. This last statement cannot be generalized for all feeding experiments. Diets enriched in eicosapentaenoic acid (e.g. fish oil) will facilitate the synthesis of trienoic prostanoids. In this series, PGI_3 retains its biological activity, while TxA_3 is inactive [20, 21, 50].

Problems of eicosanoid analysis in vivo

A great deal of confusion in eicosanoid research has been caused by inadequate analytical methods and some consideration of analytical aspects is warranted in this review. In clinical studies assessment of in vivo prostanoid activity without artifacts is a delicate undertaking. Basically this problem arises from the following factors: (a) active eicosanoids have a very short biological half-life and high potency; the resulting low levels in biological fluids require extreme analytical sensitivity [8, 11, 77, 78]; (b) a broad spectrum of prostanoid derivatives with minor structural variations, yet with major differences in their biological activity have already been identified and still more are waiting to be discovered; (c) the biosynthetic capacity of tissue greatly exceeds the actual synthesis in vivo [78]. A variety of stimuli, e.g. mechanical manipulation, will trigger the arachidonate-prostanoid cascade leading to ex vivo contamination of samples containing cells capable of synthesizing prostanoids. Thus, tissue levels of prostanoids are not meaningful as indices of in vivo product formation. These capacity-related measurements have often been misinterpreted as reflecting endogenous biosynthesis. Likewise, determinations of peripheral plasma levels of primary prostanoids (PGE_2, $PGF_2\alpha$) or their hydration products (6-keto-$PGF_1\alpha$, TxB_2) are unreliable for assessing prostanoid activity under clinical conditions [38, 89, 97]. More dependable, albeit less direct, analytical targets are the more stable enzymatic prostanoid metabolites in plasma and urine [11, 38, 94]. Plasma metabolites may reflect more acute phasic changes, while urinary metabolites integrate the overall activity. The determination of urinary excretion rates of so-called index metabolites has permitted the study of a variety of prostanoid-mediated processes, such as certain types of paraneoplastic hypercalcaemias (PGE-M) [104], systemic mastocytosis (PGD-M) [86], patent ductus arteriosus in preterm infants [6-keto-$PGF_1\alpha$ and PGE-M) [105], platelet-vascular interactions [22, 23, 84], and ovine endotoxaemia (2,3-dinor-6-keto-$PGF_1\alpha$, 2,3-dinor-TxB_2) [53].

After the discovery of primary prostanoids in human urine [31], their urinary excretion rates have frequently been employed for in vivo assessment of renal prostanoid activity. This approach appears to be justified because urine normally represents an almost cell-free medium, avoiding the ex vivo artefact, and systemically administered or generated prostanoids are excreted primarily as metabolites [9, 87, 93]. The simultaneous determination of urinary excretion rates of primary prostanoids and their metabolites has frequently been employed to assess renal as well as systemic prostanoid biosynthesis in man [10, 106].

Unfortunately, so far no useful index metabolites of lipoxygenase products, leukotrienes in particular, have been identified. This lack of a reliable analytical target for in vivo assessment of leukotriene activity explains why there is only indirect evidence for the involvement of leukotrienes in the pathogenesis of human diseases, e.g. chronic inflammatory processes and bronchial asthma.

Principally three types of eicosanoid assays have been employed: bioassay, immunoassay and gas chromatography-mass spectrometry. The bioassay plays an important role in defining the biological activity of eicosanoids. Its application in clinical research is limited by its low sensitivity, its cumbersome procedure and its failure to measure biologically inactive metabolites. The radio- and enzyme-immunoassay is more sensitive and probably more specific than the bioassay. However, there are also some serious disadvantages. The displacement of the tracer from the binding sites of the antibody can be influenced by factors unrelated to the compounds being assayed [37]. Low specificity of antiserum may lead to serious errors in reported eicosanoid levels in complex biological

fluids, such as plasma and urine [94]. For these reasons, immunoassays have to be validated by chromatographic methods, use of multiple antisera to identify cross-reactivities, and comparison with a reference method [10, 77].

In this respect, gas chromatography-mass spectrometry is currently considered as the ultimate reference assay [38]. Routine analysis of prostanoids by this physicochemical method has become much more practical in recent years thanks to several new techniques: enhanced resolving power of capillary column chromatography [18]; refined purification techniques e.g. by silica, chemo- or immunoselective cartridges [56, 72, 81]; greatly enhanced ionization efficiency of negative ion chemical ionization [8]; and tandem-mass spectrometry, which further improves selectivity and facilitates sample purification [98].

Clinical relevance of eicosanoids in early life

The following review will be restricted to studies that comply with the methodological criteria mentioned above. Too many reports have already appeared about imbalances in the prostanoid system as a pathogenetic factor in various diseases, such as diabetes mellitus, hypertension, atherosclerosis, haemolytic ureamic syndrome etc., which subsequently could not be confirmed by adequate analytical methods.

Maternal and fetal circulations

In intrauterine life eicosanoids are primarily involved in the regulation of the maternal and fetal circulations. During pregnancy PGI_2 activity rises continuously, as reflected by the urinary excretion rate of dinor-6-keto-$PGF_1\alpha$ [35]. Cigarette smoking and toxaemia in pregnancy, two conditions which may lead to the delivery of small-for-date infants, are related both to early vascular damage of the placenta and a decreased biosynthesis of PGI_2 in vivo and in vitro [35, 119]. This suggests a crucial role for this vasodilatory and anti-aggregatory prostanoid in maintaining an adequate nutritional supply to the fetus via an intact placental circulation. In addition, PGI_2 provides some tocolytic activity. Based on these observations, new concepts are currently being developed for treatment of hypertension and toxaemia in pregnancy. Whereas PGI_2 analogues are not yet under clinical investigation, a sucessful trial with low dose aspirin, which is able to block platelet TxA_2 synthesis selectively by sparing vascular PGI_2 formation, supports the concept of an imbalance between the two antagonists TxA_2 and PGI_2 in this type of hypertension [117]. Interestingly, despite extensive efforts, in no other type of hypertension could a pathogenetic role of prostanoids convincingly be demonstrated.

Apparently, eicosanoids also play an important role in modulating the fetal circulation, although, for methodological reasons, there is only circumstantial evidence. The pioneer work of Coceani and Olley [13], who showed that PGE_1 and PGE_2 are potent dilators of the fetal ductus arteriosus in hypoxia, has led to the concept that ductal patency is actively maintained by vasodilatory prostanoids in utero. Animal experiments and clinical observations of the effect of non-steroidal anti-inflammatory drugs on the fetal ductus arteriosus support this hypothesis [30, 45, 46]. When pregnant women were treated with cyclooxygenase inhibitors after the 32nd week of gestation, either for an underlying maternal disease such as rheumatoid arthritis [4] or for chronic tocolysis, premature constriction of the fetal ductus was reported [49]. However, there are also several reports on successful short-term tocolytic treatment with cyclooxygenase inhibitors between the 29th and 32nd weeks of gestation [120]. In addition to intra-uterine ductal constriction with acute right heart failure and fetal death, aspirin and indomethacin treatment in late pregnancy may also induce the development of neonatal persistent pulmonary hypertension. Mechanistically, a partially constricted ductus increases blood flow through the pulmonary circulation and may induce muscular remodelling, resulting in vascular wall hypertrophy and persistent pulmonary hypertension after birth [61, 108].

Studies with leukotriene antagonists suggest that the peptidoleukotrienes restrict pulmonary perfusion in utero under physiological conditions [109]. Whether they also play a pathophysiological role in postnatal persistent pulmonary hypertension needs to be probed with leukotriene antagonists in future studies [96, 110]. TxA_2, too, has been considered as a mediator of pulmonary hypertension associated with group B streptococcal sepsis [91]. In ovine endotoxaemia, an experimental model of the adult respiratory distress syndrome, the early phase of pulmonary hypertension was associated with a marked rise in the concentration of TxA_2 metabolites in plasma and urine and could be abolished by a thromboxane receptor antagonist [53]. However, no imbalance between TxA_2 and PGI_2 metabolites was noted in premature infants with evidence of pulmonary hypertension associated with respiratory distress syndrome and sepsis (unpublished observations). Certainly more pre- and postnatal studies are required to elucidate the role of eicosanoids in the regulation of pulmonary circulation. Pharmacologically, the vasodilatory prostanoids PGI_2, PGD_2 and PGE_1 have been administered with varying success to increase pulmonary perfusion in neonatal persistent pulmonary hypertension [80].

Patency of the ductus arteriosus

Persistent ductus arteriosus occurs as a frequent complication in premature infants. Recovery from respiratory distress syndrome diminishes pulmonary vascular resistance and precipitates a left-to-right shunt across the ductus from the descending aorta to the pulmonary artery. The frequent association of prolonged artificial ventilation and the augmented excretion of major urinary metabolites of PGE_2 and PGI_2, on the one hand, and the development of a symptomatic patent ductus, on the other, has led to the following hypothesis [105]. During artificial ventilation, pulmonary tissue is subjected to barotrauma and shear-stress, potent stimulators of pulmonary release of eicosanoids. PGI_2, one of the major pulmonary prostanoids [59], and PGE_2 will be released into the pulmonary circulation and reach the ductus arteriosus, where they maintain ductal patency as during intrauterine life. Under clinical conditions, the definite proof of this working hypothesis cannot be provided because of ethical and methodological difficulties. Nevertheless, indomethacin administration has become an approved treatment for preterm infants with patent ductus arteriosus (PDA) and is considered as a valid alternative to surgical ligation [33, 60].

Sustained PDA is of vital importance in cardiac malformations with right heart obstruction or an interrupted aortic arch in which pulmonary or systemic perfusion is inadequate. A

left-to-right or a right-to-left ductal shunt can provide temporarily sufficient perfusion of the lung or the postductal part of the body until surgical correction can be performed. In these situations, intravenous administration of PGE_1 or PGE_2 represents an effective pharmacotherapeutic intervention to maintain ductal patency [29]. The effective plasma levels of PGE_1 during systemic application ranged around 50 pg/ml (unpublished data) and were associated with the following side effects: fever, diarrhoea, hypopnoea or apnoea, and disposition to bacterial infection [63]. In addition, chronic administration of PGE_1 will lead to hyperostosis [114].

All these adverse reactions to systemically administered E-prostaglandins can readily be explained by the effect of PGE_1 or PGE_2 in the respective organ or cells and can be observed in various pathophysiological situations. Thus, endogenous PGE_2 is involved in the pathogenesis of pyrogen fever [14] and is the primary target of antipyretic treatment, maybe the most frequent paediatric drug therapy. Intractable diarrhoea, food intolerance, congenital chloride diarrhoea, and toddler's diarrhoea are thought to be consequences of stimulated endogenous prostaglandin synthesis [48, 69, 82, 92]. Besides this pathophysiological involvement in resorptive and secretory intestinal processes, prostaglandins exert a cytoprotective effect on the gastrointestinal mucosa [85]. Removal of this cytoprotection by non-steroidal anti-inflammatory drugs may cause mucosal damage and ulcers, frequent side-effects of this group of drugs [3, 52, 79, 85]. Conversely, PGE_2 analogues have become a new mode of anti-ulcer therapy. Administration of cyclooxygenase inhibitors in fetal lambs stimulates fetal breathing movements that then can be inhibited by PGE_2 in similar concentrations to those determined in our patients with PGE_1 infusions [116]. This suggests that PGE_2 suppresses fetal respiration in utero under physiological conditions. A defect in lymphocyte proliferation has been reported in Bartter syndrome [32], a disease with increased PGE_2 activity, which might be correlated to the higher infection rate observed in these patients and during PGE infusion [63]. Finally, infantile cortical hyperostosis (Caffey disease) might be the endogenous equivalent of the bone lesions induced by long-term PGE_1 and PGE_2 adminisration, a disease entity which apparently can be treated quite effectively with indomethacin.

Platelet/vessel wall interactions

The universal role of prostanoids also becomes apparent when the cyclooxygenase inhibitor indomethacin is administered in preterm infants to induce ductal constriction. Inevitably, other organs besides the ductus will participate in cycloocygenase inhibition. In this respect there was major concern about compromised haemostasis and renal function. The fear that cyclooxygenase inhibitors, by suppression of the pro-aggregatory TxA_2, might cause severe bleeding problems was based on two sets of observations. First, mothers taking aspirin in late pregnancy are at higher risk of delivering infants with impaired haemostasis and cerebral bleeding [90, 113]. Second, in vitro platelet aggregation is reversibly inhibited in infants on indomethacin treatment and bleeding time is prolonged [15]. However, only ADP-, epinephrine- and, in part, collagen-induced aggregation is mediated by TxA_2 and therefore is sensitive to cyclooxygenase inhibitors. Thrombin induces platelet aggregation directly without a prostanoid mediator [66, 74]. As long as thrombin is generated sufficiently in the coagulation system, haemostasis remains unaffected by these compounds and no major bleeding, e.g. intracranial haemorrhage, occurs [33, 65]. If there is, however, a combined defect in platelet aggregation and coagulation, serious bleeding problems can be encountered, e.g. in vitamin-K-deficient infants or in haemophilic patients [66]. In these situations, particularly aspirin, even at a low dose of 1 mg/kg per day, is contraindicated because, in contrast to other cyclooxygenase inhibitors, this compound irreversibly blocks platelet aggregation by acetylation of the platelet cyclooxygenase [88]. It is of note in this context that several studies have implicated PGI_2 and TxA_2 in the pathogenesis of peripheral vascular disease, unstable angina and myocardial infarction [22, 23, 75, 84]. These studies form the rational basis for platelet inhibitory treatment regimens like low-dose aspirin, thromboxane synthase inhibitors and receptor antagonsists that are currently being evaluated or have already shown their efficacy [44]. The implication for vascular disorders in paediatric patients, e.g. in homocystinuria or mucocutaneous lymph node syndrome (Kawasaki syndrome), merits further investigation.

Prostanoids and the kidney

Of more concern during indomethacin treatment is renal failure in preterm infants with PDA. The left-to-right shunt via the open ductus causes renal hypoperfusion. In this situation vasodilatory PGI_2 and PGE_2 synthesized in the kidney have a protective function to maintain sufficient renal perfusion and glomerular filtration rate. Indomethacin causes a shift in the vasoactive systems towards vasoconstrictor activity (e.g. the renin/angiotensin cascade) with the consequence of transient renal failure [102]. After an effective circulatory state has been re-established by ductal constriction, renal perfusion becomes independent of prostanoid activity, self-limiting the renal compromise. A similar protective effect of vasodilatory prostaglandins with respect to organ perfusion may exist in the gastrointestinal tract [52].

In addition to the vascular effects of renal prostanoids, these mediators are apparently involved in renal tubular function [95, 102]. During cyclooxygenase inhibition tubular reabsorption of sodium, potassium, calcium and particularly free water is increased with the consequence of increased extracellular volume, reduced fractional excretion of sodium, hyperkalaemia and oliguria. These marked changes in tubular function are explained by at least three mechanisms of renal PGE_2: (a) direct inhibitory effect on tubular reabsorption of electrolytes; (b) wash-out effect on the medullary osmotic gradient by vasodilation; and (c) ADH antagonism [12, 102]. Marked fetal antidiuresis has also been observed when mothers were treated with indomethacin in late pregnancy. Reduced fetal urine output results in the development of oligohydramnios [47].

As opposed to this state of iatrogenically suppressed prostanoid synthesis, excess protaglandin activity has recently been described in a so-called hyperprostaglandin E_2 syndrome [106, 107]. This disease is characterized by a history during pregnancy of polyhydramnios and premature birth, hypercalciuria with nephrocalcinosis, fever, episodic diarrhoea, isosthenuria and hypokalaemia with onset in early infancy. Biochemically, markedly stimulated renal and systemic PGE_2 production was demonstrated. Most problems in these infants can be controlled by long-term indomethacin treatment. In other renal tubular disorders, e.g. Fanconi syndrome, the effect of indomethacin has been less convincing [107].

Future aspects

There is ample experimental evidence to suggest a role for eicosanoids in other pathophysiological settings. Tissue injury as a basic principle of many disease states involves inflammatory cells that possess a great capacity for eicosanoid biosynthesis. Due to their biological profile, eicosanoids are prime candidates as mediators and modulators of cell-cell interaction in many conditions of chronic inflammation. In paediatric patients, rheumatic diseases, chronic inflammatory bowel disease [16], glomerulonephritis [77, 112], organ transplant rejection [27] might be associated with altered eicosanoid activity [73]. In particular the role of leukotrienes is not yet well defined under clinical conditions, due to the lack of appropriate analytical targets and methods. The identification of leukotrienes as the active principle of slow reacting substances of anaphylaxis [43] suggests an involvement of these potent bronchoconstrictor, vasoconstrictor, and proinflammatory agents in the pathogenesis of bronchial asthma and other types of chronic obstructive lung disease [1]. Of particular interest in this respect is chronic lung disease of prematurity (bronchopulmonary dysplasia). The development of more specific pharmacological tools, e.g. receptor antagonists, selective synthesis inhibitors and eicosanoid analogues, will enhance the capacity to dissect these complex regulatory systems. Conversely, to identify diseases that may be treated effectively by such drugs, reliable methods of eicosanoid analysis will have to be applied to clinical situations of suspected alterations in eicosanoid biosynthesis and activity.

Acknowledgements. The authors' studies referred to in this paper were supported by grants from the Deutsche Forschungsgemeinschaft (Se 263/8, Se 263/9 and Kü 544). H. W. Seyberth is a Herrmann and Lilly Schilling Professor for Medical Research from the Stifterverband für die Deutsche Wissenschaft.

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Received June 4, 1987 / Accepted June 9, 1987