REVIEW ARTICLE

Metabolic interactions between eicosanoids in blood and vascular cells

Michel LAGARDE,*† Norbert GUALDE† and Michel RIGAUD†
*INSERM U205, Bâtiment 406, INSA Lyon, F-69621 Villeurbanne Cedex, and †GRIB, Faculté de Médecine et de Pharmacie, F-87052 Limoges, France

Introduction

Eicosanoids (or icosanoids) are chemical compounds including C20 polyunsaturated fatty acids and their numerous oxygenated metabolites, the most common being arachidonic acid (5,8,11,14-eicosatetraenoic acid) and its derivatives. Three main pathways lead to these products from the fatty acid substrate. They are (i) the cyclo-oxygenase system, producing prostanoids, which include non-prostanoid derivatives like thromboxanes in addition to true prostaglandins (Samuelsson et al., 1978; Smith, 1980; Moncada, 1982), (ii) various lipoxygenase products (Needleman et al., 1986), and (iii) NADPH-dependent cytochrome P-450 epoxygenase metabolites (Capdevila et al., 1982, 1988; Snyder et al., 1983). Fig. 1 summarizes the main oxygenase pathways occurring in arachidonic acid metabolism. Although arachidonic acid is the main polyunsaturated fatty acid in blood and vascular cells, other eicosanoid precursors may arise under certain nutritional states, then providing other prostanoids and/or lipoxygenase products (Willis, 1981; Goodnight et al., 1982; Dyerberg, 1986). In addition, octadecanoids and docosanoids, deriving from C18 and C22 polyunsaturated fatty acids, respectively, may also occur during cell activation (Salem et al., 1986; Lagarde, 1988).

In recent years, cell–cell interactions via eicosanoids as well as interactions between eicosanoids themselves have been more and more accounted for. This review will focus on these aspects and will include: (i) the further metabolism by an acceptor cell of one eicosanoid produced by a donor cell, (ii) the modulation of arachidonic acid metabolism by various eicosanoids formed either in the same type of cell or another one (acceptor cell), and (iii) interactions between fatty acid precursors of eicosanoids.

Oxygenated eicosanoids as biochemical precursors

This topic concerns the metabolism of one eicosanoid by an acceptor cell after being produced by a donor cell, and could be called a cell-to-cell donation system. This will be restricted to transfers between cells of different types. Since eicosanoids are lipophilic substances, and are believed to be capable of easily crossing plasma membranes, the donation of one eicosanoid produced by one cell to the same cell type will not be considered.

In most cases, the eicosanoid transferred to another cell type for further metabolism is an oxygenated derivative of arachidonic acid. One of the first reports relating to this was the metabolism of prostacyclin (PGI2) and/or of its stable metabolite, 6-oxo-PGF1α, into 6-oxo-PGE1 by platelets (Wong, et al., 1980b), prostacyclin being not formed in platelets themselves but originating mainly from vascular endothelial cells. The process is catalysed by NAD*-dependent 9-prostaglandin dehydrogenase as described in hepatocytes (Wong et al., 1980a). The biological interest of such a transformation is to provide a prostanoid, 6-oxo-PGE1, which is much more stable than PGI2 and which however shares its biological activity. Although not derived from further metabolism by blood or vascular cells, the specific reduction of PGD2 by the liver into 9α,11β-PGF2 has to be mentioned. This stereospecific reduction is catalysed by 11-prostaglandin dehydrogenase and seems to be restricted to human liver (Liston & Roberts, 1985), whereas the liver from other species may also produce true PGF2α or 9α,11α-PGF2 (Wong, 1981; Reingold et al., 1981; Watanabe et al., 1981). The conversion of PGD2 into 9α,11β-PGF2 may be then of pathophysiological relevance since the product increases blood pressure when present in the circulation (Liston & Roberts, 1985).

Several other reports concern PGI2 production from cyclic prostaglandin endoperoxide, PGH2, of platelet origin. The first such report, from Marcus et al. (1980), referred to the contribution of stimulated platelets in providing endoperoxides as substrates for the vascular endothelial prostacyclin synthase. At the opposite, a reciprocal transfer of endothelial endoperoxides for utilization by thromboxane synthase does not seem to occur (Schafer et al., 1984). The unidirectional transfer is concerned in the pathophysiological model of atherosclerosis where an increase of urinary prostacyclin metabolites could be observed (Fitzgerald et al., 1984).

Such an increase has been attributed to platelet hyperfunctions in vivo, and is characterized by PGH2 hyperproduction. This relates to ‘basal’ production of PGH2 and it is of interest, in this respect, that PGH2 transfer from platelets to cultured endothelial cells appears more efficient under ‘basal’ conditions than under thrombin stimulation (Bordet & Lagarde, 1988). Finally, another report has described the transfer of PGH2 from platelets to de-endothelialized rabbit aorta to yield PGI2 (Papp et al., 1986), confirming the positive co-operation between platelets and the vascular wall for prostacyclin formation. In addition, leukocytes could also contribute to prostacyclin production, presumably from PGH2 of platelet origin. This has been suspected to explain the presence of prostacyclin in serum and was believed to be
Fig. 1. Main oxygenation pathways of arachidonic acid
due to monocytes as the source of prostacyclin synthase (Defreyn et al., 1982). A recent report confirmed the involvement of platelets in such a formation via lymphocytes (Wu et al., 1987). Although the latter cells are devoid of oxygenase activities (Goldyne & Stobo, 1982; Goldyne et al., 1984), their contribution might then be of interest to the prostacyclin homeostasis of circulating blood.

Other recent reports concern the platelet lipooxygenase endproduct of arachidonic acid, 12-hydroxyeicosatetraenoic acid (12-HETE). Although its biological activity outside platelets is not entirely defined, it seems to be involved in enhancement of epidermal cell proliferation (Chan et al., 1985), chemotaxis for neutrophils (Turner et al., 1975; Goetzl et al., 1980), chemokinesis for smooth muscle cells (Nakao et al., 1982), and potentiation of mononuclear pro-coagulant activity (Lorenzet et al., 1986). Its further metabolism by blood and vascular cells other than platelets may be then considered as a regulating process of such activities. Simultaneously and independently, Borgeat et al. (1982) and Marcus et al. (1982) described the formation of (5S,12S)-dihydroxy-6,10-trans-8,14-cis-eicosatetraenoic acid [(5S,12S)-diHETE] when neutrophils are incubated with (12S)-HETE or platelets with (5S)-HETE. The dihydroxylated fatty acid has been identified as a double lipooxygenase product and renamed leukotriene B4 (LTB4), as a stereo- and geometric isomer of LTB4 or (5S,12R)-dihydroxy-6,14-cis-8,10-trans-eicosatetraenoic acid. These findings do not contradict fundamentally a previous paper reporting the formation of LTB4 in leukocytes, such cells being likely to be contaminated by platelets (Lindgren et al., 1981). It is assumed that LTB4 formation from 12-HETE predominates over that from 5-HETE, accounting for the quantitative importance of 12-HETE formation in platelets as compared with leukocytes where 5-HPETE is preferentially transformed into leukotrienes rather than into 5-HETE. On the other hand, the high ratio platelets/leukocytes also favours this assumption. As for the production of LTB4, that of LTB4 requires activated leukocytes, the 5-lipooxygenase being a calcium-dependent enzyme (Jakschik & Lee, 1980). More recently, the ω-hydroxylation of 12-HETE in unstimulated neutrophils has been described (Marcus et al., 1984) and further characterized as 12(S),20-dihETE, a product of a cytochrome P-450 mono-oxygenase-dependent process (Marcus et al., 1987). This ω-hydroxylation may also occur on LTB4 to provide (5S),(12S),20-triHETE (Lindgren et al., 1981; Marcus et al., 1988). Recent investigations in our laboratory have allowed us to determine the substrate specificity of leukocyte ω-hydroxylase towards monohydroxylated fatty acids produced by platelets. This revealed that various 12-hydroxyeicosapolyenoic acids are equal substrates of the leukocyte enzyme but that 12(S)-hydroxy-5,8,10-heptadecatrienioic acid (HHT), the monohydroxylated byproduct of cyclooxygenase activity, was virtually not ω-oxidized. This agrees with a similar quasi-absence of ω-hydroxylated 15-HETE, and leads to suggest that the position of the hydroxyl group, closer to the ω end in the latter two compounds, might be crucial for enzyme activity (Guichardant & Lagarde, 1988).

Although transformation of the precursor is not due to an acceptor cell, the example of specific metabolism of 12- and 5-HPETE by blood plasma haemoproteins must be stated. It has been shown that incubating 12-HPETE with haematin or haemoglobin provokes its specific rearrangement into hydroxyepeoxy derivatives, 8-hydroxy- and 10-hydroxy-11,12-epoxyeicosatrienoic acids (Pace-Asciak, 1984a,b). Similarly, but with a different mechanism, 5-HPETE is isomerized into leukotriene A4 (LTA4) by haemoglobin (Radmark et al., 1984). The physiological relevance of such isomerization is however questionable since hydroperoxide precursors are likely to be trapped very efficiently in the corresponding donor cell, e.g. by the glutathione-dependent peroxidase associated with the lipooxygenase pathway in platelets (Bryant et al., 1982) and by both a similar peroxidase and by leukotriene synthase activities in leukocytes (Needleman et al., 1986).

The most recent findings relating to eicosanoid further metabolism by other cell types concern leukotrienes and especially LTA4 (5,6-epoxy-7,9-trans-11,14-cis-eicosatetraenoic acid). This epoxy derivative of arachidonic acid is a pivotal precursor in the biosynthesis of other leukotrienes (Borget & Samuelsson, 1979). This labile compound ( Fitzpatrick et al., 1982) can be very efficiently transformed into LTB4 by human erythrocytes which possess a cytosolic epoxide hydrolase (Fitzpatrick et al., 1984; McGee & Fitzpatrick, 1986). In addition to lymphocytes, erythrocytes represent another example of cells virtually devoid of dioxygenase activity (Schrier, 1967; Kobayashi & Levine, 1983), which are however able to generate lipid mediators through cell–cell interactions.

Further metabolism of LTA4 into peptidoleukotriene, LTC4 [(5S)-hydroxy-(6R)-S-glutathionyl-7,9,11,14-eicosatetraenoic acid], by vascular endothelium, which is unable to produce LTA4 itself (Gorman et al., 1985; Miller et al., 1985), has been described (Feinmark & Cannon, 1986). Similar conversion has been observed in platelets, which also fail to synthesize LTA4 (Maclouf & Murphy, 1988). In both cell populations, the ability to produce LTC4 appears quite substantial, making the process of physiological relevance. The potentiation of adrenaline-induced platelet aggregation by LTC4 (Mehta et al., 1986) reinforces the biological interest of the platelet contribution to LTC4 formation from LTA4 of leukocyte origin. Vascular smooth muscle cells have also been recently reported to be able to convert LTA4 from other cellular origins into LTC4 (Feinmark & Cannon, 1987). This may be particularly important considering that such a transcellular LTA4 metabolism leads to the generation of the vasoconstricting agent LTC4 ( Drazen et al., 1980; Greenwald et al., 1984) in the proper target tissue. Finally, the vascular wall (Piper & Galton, 1984) as well as macrophages (Nagaki & Yamashita, 1987), having the capacity to convert LTC4 into LTD4 and LTE4, could contribute to producing LTD4 and LTE4, derived from LTA4 and LTD4, derived from neutrophils. The overall cell–cell interactions via these processes are summarized in Fig. 2.

Modulation of arachidonic acid metabolism by eicosanoids

This part of the review will concern various eicosanoids of which the synthesis is modified by other eicosanoids not convertible into the former. This modulation may concern the same cell types as well as neighbouring cells of different populations.

Numerous papers have described the biological effect of prostanoids and the reader can refer to the reviews from Samuelsson et al. (1978) and Needleman et al.
Fig. 2. Some examples of interaction between blood and vascular cells via eicosanoids transformed in the acceptor cell

Further abbreviation: AA, arachidonic acid.

(1986). In the context of the present review, it may however be useful to restate a common mechanism of several prostaglandins like PGD₂, PGE₂ and PGI₂ in altering cell cyclic AMP via adenylate cyclase stimulation, and subsequently modulating arachidonic acid release at the phospholipase A₂ level, depending on the target cell. This has been well documented in human platelets where PGD₂ and PGI₂ stimulate adenylate cyclase (Mills & MacFarlane, 1974; Gorman et al., 1977), although these prostaglandins have different receptor sites (Schafer et al., 1979). Cyclic AMP being a potent inhibitor of platelet liberation of endogenous arachidonic acid (Lapetina et al., 1977; Minkes et al., 1977), PGD₂ and PGI₂ will inhibit eicosanoid synthesis in platelets. The physiological relevance of such an inhibition by PGD₂ is reinforced in considering that this prostaglandin is the main cyclooxygenase product of human mast cells (Lewis et al., 1982). PGI₂ has also been reported to inhibit its own formation in vascular endothelial cells with a similar mechanism (Brotherton & Hoak, 1982), but this was controversial (Brotherton et al., 1982). Finally, as PGE₂ exhibits a biphasic effect on platelet adenylate cyclase activity [an inhibition at low concentrations (below $5 \times 10^{-3}$ M) and an activation at higher concentrations (Salzman et al., 1972; Malmsten et al., 1976)], it would act accordingly on the liberation of endogenous arachidonic acid, although the facilitation of such a liberation by decreasing platelet cyclic AMP is not proved.

In addition to the effect of prostaglandins, that of lipoxygenase products has been more recently investigated and seems particularly promising. First, it has been shown that 15-HETE, the end-product of the 15-lipoxygenation of arachidonic acid, is an inhibitor of leukotriene synthesis in polymorphonuclear leukocytes, acting at the 5-lipoxygenase step (Vanderhoek et al., 1980a). The potency of 15-HETE towards 12-lipoxygenase is however 10-fold higher than towards 5-lipoxygenase. The effect on 12-lipoxygenase is shared by some other 15-lipoxygenase products, the potential of inhibition being increased with the number of cis double bonds of the inhibitors (Mitchell et al., 1984). The inhibitory effect of 15-HETE on 5-lipoxygenase might depend on the target cell, since an opposite effect has been observed in a mast/basophil cell line and interpreted as a direct activation of a cryptic 5-lipoxygenase (Vanderhoek et al., 1982). Another example of stimulation has been given in human neutrophils, where both 5-HETE and LTB₄ potentiate their own formation as well as that of platelet-activating factor (PAF), the concomitant product of the stimulated cells (Ramesha & Pickett, 1986). It has been concluded in this case that 5-HETE and LTB₄ may enhance the expression of phospholipase A₂ (Billah et al., 1985), as reported previously in stimulated HL-60 granulocytes (Siegel et al., 1982). This contrasts with data obtained with normal platelets and neutrophils showing the inhibition of cell phospholipase A₂ activity by 5-, 12- or 15-HETE (Chang et al., 1985). The physiological relevance of the latter data is however difficult to evaluate, since the IC₅₀ observed for HETEs reached $5 \times 10^{-5}$ M.

As compared with the corresponding HETEs, the inhibitory effect of hydroperoxy derivatives is usually higher. As an example, 12- and 15-HPETE have been compared with 12- and 15-HETE on arachidonic acid-derived eicosanoid production in macrophages (Humes et al., 1986). Hydroperoxy derivatives appear as irreversible inhibitors of both cyclooxygenase (PGE₂ production) and lipoxygenase (LTC₄ production), whereas the corresponding hydroxylated compounds exhibit re-
versible effects. This could be explained by destructive effects of hydroperoxides on oxygenases, at least at relatively high doses (Siegel et al., 1979a). The destruction has been assumed to be due to oxygen radicals generated from hydroperoxides, and has been well documented with cyclo-oxygenase as the target (Ham et al., 1979; Kuehl & Egan, 1980; Egan et al., 1981). This concept has to be taken with caution, since low concentrations of hydroperoxides oppositely enhance cell oxygenase activities (Hemler et al., 1978; Lands, 1984). This is illustrated by platelet 12-lipoxygenase which is stimulated by its hydroperoxide product, 12-HPETE (Siegel et al., 1979b).

Similarly, 12-HPETE stimulates leukocyte 5-lipoxygenase product formation, LTC₄ in neutrophils (Maclouf et al., 1982) and LTC₄ in monocytes (Maclouf et al., 1985). It may be however suspected that the potentiating effect of 12-HPETE is more likely to occur in the mother cell instead of another cell type, since normal platelets, from which it originates, convert it efficiently to 12-HETE via the glutathione peroxidase associated with 12-lipoxygenase. The pathophysiological relevance of the paracrine effect of 12-HPETE cannot be however excluded in some platelets of depressed antioxidant status, as in aging (Vatassery et al., 1983; Vericel et al., 1988) and diabetes (Watanabe et al., 1984). In addition, the stimulating effect of hydroperoxides might be crucial for eicosanoid formation from other precursors than arachidonic acid, and will be reviewed in the next paragraph.

Some cytokine effects of leukotrienes and lipoxins have also been reported on the oxygenated metabolism of arachidonic acid. This has been first reported in macrophages where LTC₄ stimulates prostaglandin release (Feuerstein et al., 1981), and it has since been well documented with endothelial cells as the target. In cultured human endothelial cells, LTC₄ stimulates prostacyclin synthesis (Benjamin et al., 1983; Cramer et al., 1983). This stimulation seems to depend on LTC₄-specific receptors on the cell, suggesting it is subsequent to phospholipase A₂ activation. As a matter of fact, McIntyre et al. (1986) have found that LTC₄-stimulated endothelial cells synthesize PAF concomitantly, as a co-product of phospholipase A₂ activation. Since LTC₄ is produced in endothelium from LTA₄ of leukocyte origin (Feinmark & Cannon, 1986), we may consider that leukocyte adherence to the vessel wall might be coupled with prostacyclin formation in the endothelium. Finally, a recent report has described the potentiation of thromboxane formation in human polymorphonuclear leukocytes by lipoxin A₄ (55,6R,155)-trihydroxy-7,9,13-trans-11-cis-eicosatetraenoic acid (Conti et al., 1987) a newly discovered leukocyte double lipoxygenation (15-then 5-lipoxygenase) product of arachidonic acid (Serhan et al., 1984).

Although not belonging to the eicosanoids, the 13-hydroxy derivative of linoleic acid must be accounted for in the context of this review. (13S)-Hydroxy-9-cis-11-trans-octadecadienoic acid (‘13-HODE’), synthesized by endothelial cells (Buchanan et al., 1985) and leukocytes (Claeys et al., 1985; Soberman et al., 1985). Recent reports have shown that this ‘octadecanooid’ may inhibit the formation of 5-lipoxygenase products in leukocytes (Camp & Fincham, 1985), may stimulate prostacyclin synthesis in endothelial cells (Setty et al., 1987a), and may depress thromboxane and enhance 12-HETE formation in platelets (Setty et al., 1987b). The mechanisms of these different effects are unknown, except for the stimulation of prostacyclin synthesis which seems to be related to endothelial phospholipase A₂ activation.

**Interactions between fatty acid precursors**

This section concerns both the antagonism and synergism between various fatty acids which may be potential substrates of cyclo-oxygenase and/or lipoxygenases. Apart from arachidonic and linoleic acids, most of the other polyunsaturated fatty acids, which may be substrates of dioxygenases, are solely of nutritional value in blood and vascular cells and previous reviews can be referred to for their biological interest (Willis, 1981; Goodnight et al., 1982; Dyerberg, 1986). The present review will be restricted to some points relevant to biochemical interactions between these fatty acids.

Data concerning cyclo-oxygenase activity have been mostly known for several years, at least for the three classical substrates, dihomo-γ-linolenic acid (8,11,14-eicosatrienoic), arachidonic acid (5,8,11,14-eicosatetraenoic) and timnodonic acid (5,8,11,14,17-eicosapentaenoic), the precursors of the monoene, diene and triene prostanoïds, respectively (Needleman et al., 1976). The interaction can be summarized by the inhibition of arachidonic acid cyclo-oxygenation by dihomo-γ-linolenic acid (Kernoff et al., 1977), and by timnodonic acid (Needleman et al., 1979), in a competitive way. More recently, two docosapolyenoic acids have been recognized as additional substrates of cyclo-oxygenase. They are adrenic acid (7,10,13,16-docosatetraenoic) and 4,7,10,13,16-docosapentaenoic acid. The former has been described as the precursor of dihomo-PGI₂ in endothelial cells (Campbell et al., 1985) and of dihomo-thromboxane in platelets (Van Rallions et al., 1985), and the latter as the precursor of Δ⁴-di-homo-prostanoids (Milks & Sprecher, 1985). These studies showed that adrenic acid appears as a potent inhibitor of arachidonic acid cyclo-oxygenation, presumably via a competitive process. A competitive inhibition of LTB₄ formation by timnodonic acid has also been recently observed (Lee et al., 1984).

A number of C₁₈, C₂₀ and C₂₂ polyunsaturated fatty acids are potential substrates of blood and vascular cell lipoxygenases, then providing a cohort of octadecanoids, eicosanoids and docosanoids, respectively. The biochemical regulation of their synthesis has not been yet fully investigated, but such a regulation can be proposed, essentially in platelets and endothelium. Like the lipoxygenation of arachidonic acid, which is potentiated by its own product, 12-HPETE (Siegel et al., 1979b), that of some other fatty acid substrates is highly sensitive to the peroxide status of the cell, in relation to the oxygenation of arachidonic acid. As a matter of fact, both the platelet cyclo-oxygenation and lipoxygenation of dihomo-γ-linolenic and timnodonic acids are markedly potentiated by arachidonic acid (Boukhchache & Lagarde, 1982), apparently through 12-HPETE (Morita et al., 1983; Croset & Lagarde, 1985). This agrees with the requirement of a certain peroxide status for the oxygenation of some polyunsaturated fatty acids, of which timnodonic acid has been mostly studied (Lands, 1984). In blood and vascular cells, arachidonic acid appears as the physiological potentiator in providing specific peroxides. Amongst various polyunsaturated fatty acids, timnodonic acid seems to be entirely dependent on such peroxides, whereas the dependence of others is weaker. As
an example, the lipooxygenation of the homologue of timnodonic acid, cervonic acid (4,7,10,13,16,19-docosahexaenoic), is also enhanced by arachidonic acid, but, in contrast with timnodonic acid, it seems able to provide some peroxides by itself, and can indeed partially replace arachidonic acid for potentiating the oxygenation of timnodonic acid (Croset et al., 1988).

Finally, similar potentiations could be observed for the vascular endothelial synthesis of PGI₃ and dihomo-PGI₂ from timnodonic and adrenic acids, respectively. Arachidonic acid, as well as its 15- lipooxygenase product, 15-HPETE, were responsible for these stimulations (Bordet et al., 1986, 1988). Fig. 3 summarizes some interactions between fatty acid precursors of oxygenated derivatives.

Conclusion

Metabolic interactions between eicosanoids represent new trends of research in the field of lipid mediators. They are particularly relevant in blood and vascular cells where multiple cell types may interact during their functions. The interactions stated in this review may certainly be extended to various other compounds, but all need to be specified by further studies of their mechanisms, especially concerning the modulation of arachidonic acid metabolism by lipooxygenase products. In addition to those specifications, an overall view of physiological and pathophysiological states should be taken into consideration to ensure the biological relevance of the findings.

References

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