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INTERFERONS, INTERLEUKINS, VIRUS-HOST INTERACTION: RELATION TO LEUKOTRIENES AND OTHER LIPOXYGENASE DERIVATIVES OF THE ARACHIDONIC ACID

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Summary. — The leukotrienes and other lipoxygenase-derived metabolites of the arachidonic acid were proved to possess various biological activities and to participate in a number of pathological states and diseases, especially those associated with inflammatory processes and with altered immune response. The present paper reviews the role of these eicosanoids in the regulation of natural-killer cell activity and in production and action of some cytokines including interferons. Furthermore, the participation of the arachidonic acid lipoxygenase metabolism in the virus-host interaction and the relation of these findings to some experimental and human diseases is discussed.

Key words: *interferons*; *interleukins*; *virus-host interaction*; *leukotrienes*; *lipoxygenase metabolism of the arachidonic acid*; *diseases*; *multiple sclerosis*

Metabolites of the arachidonic acid (AA) represent an ubiquitous system involved both in physiological regulation and in pathological processes. More detailed understanding of the lipoxygenase pathways of AA and the discovery of leukotrienes in the late 70th have provided new looks at their metabolism. Leukotrienes were recognized as potent mediators of various cellular functions including participation in the immune response, and moreover, these compounds were demonstrated to play a significant part in number of diseases and pathological states (Bach, 1984; Ford-Hutchinson, 1984; Higgs and Moncada, 1985; Rola-Pleszczynski, 1985; Thorsen, 1986). Growing evidence has been obtained on the relation of lipoxygenase-derived eicosanoids to the production and action of some cytokines including interferons and to the regulation of natural killer (NK) cell activity directed both against tumour and against virus-infected cells. The leukotrienes and lipoxygenase AA metabolism were also proved to participate in some events associated with the host response to the viral infection.

Table 1. Metabolic pathways and cellular systems associated with lipoxygenase metabolism of the arachidonic acid

Calcium ion homeostasis	(Brash *et al.*, 1984; Dornand *et al.*, 1987; Fink *et al.*, 1985*b*; Parker, 1984)
Cyclooxygenase pathway of the arachidonic acid metabolism	(Bonta *et al.*, 1985; Busija and Leffler, 1986; Fink *et al.*, 1985*b*; Thomson *et al.*, 1982)
Energy metabolism and redox systems	(Ahnfelt-Rønne and Olsen, 1985; Ball *et al.*, 1986; Brash *et al.*, 1984; Czaki *et al.*, 1986; Tahakama *et al.*, 1985)
Cyclic nucleotide system	(Jondal *et al.*, 1985; Reibman *et al.*, 1986; Shermann *et al.*, 1988; Thomson *et al.*, 1982)
Protein kinase C	(Dornand *et al.*, 1987; Jondal *et al.*, 1985)
Cellular microtubular apparatus	(Reibman *et al.*, 1986)

Arachidonic acid metabolic pathways

Arachidonic acid (5,8,11,14-eicosatetraenoic acid) is mobilized from membrane phospholipides by phospholipases A2 and C. Free AA may then be metabolized by oxygenating enzymes. Cyclooxygenase cytalyses the production of cyclic endoperoxides and this pathway further leads to the formation of prostaglandins, prostacyclin and thromboxanes. Lipoxygenase enzymes catalyze the reaction of the polyunsaturated substrate with molecular oxygen to form hydroperoxy fatty acids. On the 5-lipoxygenase pathway (i.e. oxygen bound in the 5-position) the 5-hydroperoxyde is converted to the labile 5,6-epoxy derivative leukotriene (LT) A_4, which serves as a common intermediate for further leukotriene synthesis, being transformed either to LTB_4 and related products or, after conjugation with the tripeptide glutathion, to the sulphopeptide leukotrienes C_4, D_4, and E_4 (Bach, 1984; Brash, 1984; Parker, 1984; Higgs and Moncada, 1985; Rola-Pleszczynski, 1985; Thorsen, 1986). Another most recently recognized group of the lipoxygenase-derived products of the AA cascade is formed by lipoxins which are generated from the incubation of 15-hydroperoxy eicosatetraenoic acid with stimulated human leukocytes (Ramstedt *et al.*, 1985; Rokach and Fitzsimmons, 1986).

Some other polyunsaturated fatty acids ("alternative fatty acids") could both enter the described metabolic pathways and interact with the synthesis and/or action of the AA derivatives. The omega-3-polyunsaturated fatty acids — docosahexaenoic and eicosapentaenoic — contained in fish oil are the most investigated representatives of this fatty acid group (Ford-Hutchinson, 1986). In conclusion of this brief outline of AA metabolism it is worth emphasizing that although the scope of this review is predominantly focused on the lipoxygenase AA pathways and especially on leukotrienes, this issue must be seen in a wider context. Table 1 summarizes other meta-

bolic systems connected with the synthesis and action of leukotrienes and of other lipoxygenase derivatives of AA.

Leukotrienes, natural killer cell activity, interleukins, and interferons

The research into the lipoxygenase-derived metabolites of AA has demonstrated that, in addition to other biological activities, these of eicosanoids participate in the regulatory network of the immune and inflammatory processes (for review see e.g. Rola-Pleszczynski, 1985; Thorsen, 1986) and the lipoxygenase derivatives have been proved not only modulate but also mediate various immune functions including those involved in anti-viral host defense. Among them, the NK activity and the production and action of immunoregulatory cytokines — interleukins 1 and 2 (IL-1,2) and interferons (IFs) have been repeatedly reported to be interconnected with the AA lipoxygenase metabolism.

The process of NK cell-mediated cytotoxicity involves several distinct phases and it is regulated by a complex of factors. The possibility of participation of the lipoxygenase branch of the AA metabolism in these regulations become evident from the experiments in which the effect of the compounds interfering with the AA metabolism was investigated. In most of these studies the lipoxygenase inhibitors reversibly reduced or inhibited NK cell activity in non-toxic concentrations, while the cyclooxygenase inhibitors did not display such effect. Further research was directly focused on the action of synthetic leukotrienes. In some studies LTB_4 not only enhanced NK cell activity directed both against tumour targets and to the virus-infected cells, but also reconstituted the NK activity depressed by lipoxygenase inhibitors (Rola-Pleszczynski *et al.*, 1983; Seaman and Woodcock, 1984; Sibbit *et al.*, 1984; Rosii *et al.*, 1985; Jondal *et al.*, 1986; Leung and Ip, 1986). An analogical effect was associated with some LTB_4-related derivatives of the AA metabolism (Rossi *et al.*, 1985; Bray and Brahmi 1986; Jondal *et al.*, 1986). Dependence similar to NK activity was demonstrated also for the lymphokine-activated killing; the lipoxygenase inhibitors suppressed the IL-2 dependent killing function of peripheral blood mononuclear cells against NK-resistant targets and this suppression could be reversed by addition of LTB_4 to the effector-target suspension (Sibbit *et al.*, 1986).

These data strongly suggest that cell-mediated killing and especially NK cell activity required lipoxygenation of AA. Whether this dependence is strictly related to the effector cell or whether other leukocyte population and/or thrombocytes are capable of lipoxygenation of AA remains to be elucidated. However, it does not appear likely that the main role of leukotrienes in the cell-mediated killing consists only in the influence on effector-target binding (at least for most of the target cells tested) and that also the target cells seem to be unaffected by the lipoxygenase derivatives (Bray and Brahmi, 1986). Jondal *et al.* (1986) supposed that the lipoxygenase-derived eicosanoids may function as a second messenger for activating a target molecule as cyclic nucleotide cyclases and/or protein kinase C. Leung

and Ip (1986) considered the lipoxygenase activity to be necessary for NK activation induced by interferon (IFN) and Rola-Pleszczynski and Gagnon (1986) suggested that LTB_4 acts in the process of natural killing through induction of interferon or through an IFN-like effect. The latter authors concluded that LTB_4-dependent events may play an important role in host defence against tumour and virus-infected cell. In contrast to leukotrienes, lipoxins — the novely recognized derivatives of AA lipoxygenation — were shown to abrogate the activity of human NK cells at submicromolar concentrations by mechanism unrelated to cyclic nucleotides or to the target-cell binding (Ramstedt *et al.*, 1985).

An important system involved in the regulation of NK activity is represented by the cytokines such as IL-1 and-2 and IFN (Peters and Heidenreich, 1980; Rola-Pleszczynski and Gagnon, 1986; Dinarello and Mier, 1987 Skurkovich *et al.*, 1987). In analogy to natural killing, IL-1 and IL-2 production was shown to be inhibited by lipoxygenase inhibitors (Kato and Murota, 1985; Rola-Pleszczynski and Lemaire, 1985; Kato *et al.*, 1986). The latter did not interfere with IL-2 receptor expression or with acquisition of lymphocyte reactivity to IL-2 (Kato and Murota, 1985; Kato *et al.*, 1986). The exogenous LTB_4 and to a lesser extent LTD_4 were proved to enhance IL-1 production by lipopolysacharide-stimulated human monocytes and, furthermore, LTB_4 induced the IL-1 production by monocytes untreated by other stimulators. Indomethacin together with LTB_4 contributed to the augmentation of IL-1 production (Rola-Pleszczynski and Lemaire, 1985). The interrelation between leukotrienes and lipoxygenase AA metabolism in general on one hand and the K-dependent celullar events on the other hand was confirmed by other authors (Farrar and Humes, 1985; Atluru and Goodwin, 1986; Jordan *et al.*, 1986). Moreover, Goodwin *et al* (1986) found that the inhibition of T cell proliferation and IL-2 production by corticosteroids and by the 5-lipoxygenase inhibitors may be completely reversed by the addition of LTB_4 but LTB_4 alone did not bring about IL-2 production or proliferation of resting lymphocytes. Thus, LTB_4 production appears to be a necessary but per se not sufficient step in phytohaemagglutinin-induced IL-2 production (Goodwin *et al.*, 1986). Dornand *et al.* (1987) using lymphoid cell lines found that the role of lipoxygenase AA metabolites played in the IL-2 synthesis is related to the rise of intracellular calcium and to processes associated with the protein kinase C activation.

Regarding the mutual functional interrelationship between IL-1 and-2 and interferon mediators, the attention of the investigators was focused on the role of lipoxygenase metabolism also in the IFN associated immune regulations. LTB_4 was shown to enhance markedly the IFN gamma and IL-2 productions by $T4^+$ human lymphocytes (Rola-Pleszczynski *et al.*, 1986) and, moreover, the leukotrienes B_4, C_4, and D_4 were capable to replace IL-2 in inducing the IL-2 mediated production of IFN gamma (Johnson and Torres, 1985). Rola-Pleszczynski *et al.* (1987) demonstrated that LTB_4-pulsed T cells can modulate lymphocyte proliferation and monocyte IL-1 production by secreting IFN gamma. The effect of LTB_4 upon the IFN gamma production was dependent on the phenotype of the lymphocytes; the IFN production

was enhanced in the $T4^+$ cells and suppressed in $T8^+$ cells. The authors proposed that IFN gamma acts as a second messenger of the LTB_4-dependent immunoregulatory network.

Rather controversial data were obtained on the effect of IFN on leukotriene production. In the experiments of Ito *et al.* (1987) the pretreatment with IFN alpha augmented the production of LTB_4 in murine macrophages stimulated by opsonized zymozan. IFN gamma did not possess this capability. Boraschi *et al.* (1987) found IFN alpha, beta and gamma to depress leukotriene production in mouse peritoneal macrophages stimulated with zymozan or with the calcium ionophore A23187. IFN gamma inhibited the formation of LTA_4 (and thus the synthesis of both the LTB_4 and LTC_4), whereas IFN alpha and IFN beta inhibited only the LTC_4 production by unidentified mechanism. The concentration of IFN gamma required for the inhibition of LTC_4 production were substantialy higher than that needed for the activation of various macrophage functions. The dose dissociation between leukotriene stimulatory and inhibitory effects is believed to represent a self regulating feedback mechanism (Boraschi *et al.*, 1987).

The relation of lipoxygenase metabolism to IFN-associated processes was also indicated by the studies using chemiluminiscence and leukocyte adherence inhibition assays which were proved to be associated, among other metabolic systems, with the AA lipoxygenation. As found by Fink *et al.* (1985*a*), Hamman and Hopf (1986) and Ito *et al.* (1985) IFN priming may significantly contribute to cellular mechanisms involved both in chemiluminiscence and in leukocyte adherence inhibition.

Although IL-1, IL-2, and IFN mediators are the most studied cytokines in the relation to the AA lipoxygenase metabolism, the possibility of such association has recently been indicated also for some other cytokines — tumour necrosis factor (TNF) and granulocyte-macrophage colony-stimulating factor (GM-CSF) (Silberstein *et al.*, 1986; Roubin *et al.*, 1986; DiPersio *et al.*, 1988). These mediators alone do not promote the release of leukotrienes as proved with human neutrophils and eosinophils, but they prepare (or "prime") the leukocytes stimulated by secondary stimuli for enhanced AA release and LTB_4 production and for other biological activities. Although the mechanism of this phenomenon remains not quite clear yet, its biological significance seems to consist in activation of effector leukocytes in desirable sites and time without inappropriate general activation of the immune and/or inflammatory response what might have a detrimental influence upon the host organism (DiPersio *et al.*, 1988).

Leukotrienes involved in virus-host interactions and their role in virus infection

The processes leading to cell injury and to other pathogenetic events caused by a viral infection and/or by altered immune response to it represent another interesting aspect of the reviewed topic. Since leukotrienes were shown to mediate a number of pathological processes, their role in the host-virus interaction has recently become research subject of several groups.

In frog virus-3-induced hepatitis of rats an enhanced generation of peptido-leukotrienes was described *in vivo*. Furthermore, both the 5-lipoxygenase and the dual cyclooxygenase/lipoxygenase inhibitors were able to reduce the hepatocellular injury caused by the virus infection. These results suggest that leukotrienes act as primary mediators in the frog virus-3-induced hepatitis (Hagmann *et al.*, 1987). In another experimental model, Moshonov *et al.* (1986) observed cardiac myolysis in guinea pigs senzitized with vesicular stomatitis virus following challenge with the virus antigen. The cardiomyolysis was associated with the production of peptidic leukotrienes and it could be to a great extent prevented by the combination of cyclooxygenase/lipoxygenase inhibitor and H1 histamine receptor antagonists, and, to a lesser extent, by the cyclooxygenase/lipoxygenase inhibitor alone. The authors concluded that myolysis was caused by leukotrienes produced in response to the challenge with viral antigen.

Another field of medicine, where the association between viral infection and leukotriene-dependent pathogenetic events has been investigated, is the respiratory tract infection. Sulphopeptide leukotrienes were proved to be potent bronchoconstrictors, stimulators of musocal production within the respiratory tract and they were demonstrated to induce pulmonary oedema, probably due to their ability to impair the microvascular permeability (Marom *et al.*, 1982; Kay, 1983; Bach, 1984; Ford-Hutchinson, 1984). The relation of viral infection to the leukotriene-associated events in bronchial asthma was proposed by Fink *et al.* (1985*a*). Volovitz and co-authors (1987) focused their attention to the LTC_4 release into nasopharyngeal secretion during virus infection of the respiratory tract. They found that the presence of respiratory syncytial virus-specific IgE may be in relation to the LTC_4 release into nasopharyngeal secretions (Volovitz *et al.*, 1987). In further studies they compared the LTC_4 concentration in nasopharyngeal secretions in children with naturally acquired respiratory illness and in healthy controls. The presence and concentration of LTC_4 was associated with acute virus infection. The viral agents were identified as parainfluenza virus type 3, respiratory syncytial virus and influenza virus type A. Evidence for active viral disease appeared to be critical for LTC_4 production. The authors supposed that the development of virus-induced bronchospasm may be related to musocal virus-cell interaction and to release of active mediators such as LTC_4.

In this context should be mentioned that although the ethiopathogenesis of multiple sclerosis (MS) remains not fully understood, results of certain epidemiological, virological and immunological studies support the hypothesis that an environmental factor possibly infectious in nature and the impaired immune response may be involved (Cook and Dowling, 1980; Kurtzke *et al.* 1980; Ellison *et al.*, 1984; McDonald *et al.*, 1984; Sibbley *et al.*, 1985; Waksman, 1985; Cook *et al.*, 1986). Some indirect evidence has emerged for the role AA lipoxygenase metabolism in the pathogenesis of MS. As mentioned above, leukotrienes are important regulators of interleukin and IFN metabolism, mediators of NK activity and of other immune functions which were consistently shown to be defective in MS (Haar *et al.*,

1983; Neighbour, 1984; Dore-Duffy *et al.*, 1985; Hirsch *et al.*, 1985; Salonen *et al.*, 1985; Vervliet *et al.*, 1985; Selmaj *et al.*, 1986; Hamman and Kopf, 1986; Braakman *et al.*, 1986; Ilonen *et al.*, 1987). The role of cytokines, especially that of tumour necrosis factor in the demyelination in MS was intensively studied (Selmaj and Raine, 1988). Furthermore, leukotrienes act as potent mediators of chemotaxis, chemokinesis, and inflammatory infiltration and as potent stimulators of phagocytosis (Ford-Hutchinson, 1984; Bonta *et al.*, 1985; Higs and Moncada, 1985; Thorsen, 1986). These compounds also significantly contribute to an increased permeability of postcapillary venules, to the impairment of the haematoencephalic barrier and they participate in the development of oedema of the CNS structures (Black and Hoff, 1985; Black *et al.*, 1985; Mayhan *et al.*, 1986). Most of the mentioned processes were reported to be involved in plaque formation and demyelination in MS (Waksman, 1984; Troiano *et al.*, 1985; Silberg, 1986) and as mentioned above in some experimental systems and human diseases the leukotrienes and other lipoxygenase AA derivatives represent the mechanism which mediate the virus-dependent cell injury due to both the direct virus-cell interaction and to the host response to virus infection.

In conclusion, the quickly developing research of the AA lipoxygenase metabolic cascade provides new insights into the mechanisms of the immune response, virus host interaction and pathogenesis of certain human diseases.

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