

Lipoperoxides in thrombosis and atherosclerosis

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Editorial

The subcommittee on "Lipids, prostanoids and thrombosis", one of the working parties of the European Thrombosis Research Organization (ETRO), recently organized its fifth meeting in Bad Ischl, Austria. Every second year this subcommittee, chaired by Prof. A. Nordøy, Tromsø, Norway, tries to bring together active experts in the field of (dietary) lipids, prostanoids and (arterial) thrombosis for an informal exchange of ideas, to discuss recent developments, and to explore new areas of interest.

At the first day of this two-day's workshop the possible role of lipid peroxidation in thrombosis was discussed in an attempt to discriminate between fact and fiction. The subject was introduced by two well-known experts in this field: *Slater* and *Gutteridge* (both from London, England) who also pointed out that although peroxidation of lipids is mainly considered deleterious, it has also been shown to be essential for the initiation of certain biochemical reactions, required for physiological regulatory processes. The contributions by *Lagarde* (Lyon, France) and *Buchanan* (Hamilton, Canada) illustrated this regulatory role of lipid peroxidation for the enzymatic oxygenation of polyunsaturated fatty acids and for platelet-vessel wall interactions, respectively.

Although direct evidence for the involvement of lipid peroxidation in ischaemic cardiovascular

disease is almost lacking, indirect indications have repeatedly been obtained. Thus *Loeper* (Paris, France) demonstrated that hyperlipidaemia and overt atherosclerosis are associated with increased plasma levels of MDA (a product of lipid peroxidation), whereas the levels of two "protective enzymes" were either decreased (superoxide dismutase) or unaltered (glutathion peroxidase). Apart from these enzyme activities, dietary antioxidants (e.g. Selenium and the Vitamins A, C and E) may be important to keep lipid peroxidation within "safe" limits. *Gey* (Basle, Switzerland) reported on a large-scale international epidemiological study, the results of which strongly indicate a negative relationship between the "antioxidant status" of the blood and the incidence of ischaemic heart disease. In a prospective case-control study, however, *Kok* (Rotterdam, the Netherlands) did not observe an association between low serum levels of selenium, vitamin E and vitamin A and cardiovascular mortality. This negative finding contrasts with many studies demonstrating the involvement of lipid peroxidation in various mechanisms implicated in atherogenesis and thrombogenesis. *Barrowcliffe* (London, England) provided evidence that auto-oxidation products of polyunsaturated fatty acids generate a procoagulant activity on the surface coat of chylomicra and may, thereby, contribute

to an increased thrombotic risk. As demonstrated by *v. Hinsbergh* (Leiden, the Netherlands) very low and low density lipoproteins in plasma can be (per)oxidized by endothelial cells or macrophages, as a result of which these lipoproteins become toxic for cells and promote atherogenesis. *Gryglewski* (Cracow, Poland) pointed to the importance of the endothelium-derived relaxing factor (EDRF) for maintaining normal vascular tone. He documented his working hypothesis that EDRF is rapidly inactivated by the reducing potency of superoxide anions. Since the oxidizing potency of other free radicals inhibit the formation of prostacyclin, uncontrolled lipid peroxidation is likely to abolish important "defensive" activities of intact endothelium.

These detrimental effects of lipid peroxidation requires the presence of regulatory mechanisms to control the peroxide tone. In this context physiological antioxidants may be expected to be of great importance. The role of Selenium was discussed by *Parnham* (Cologne, FRG) who also demonstrated that Ebselen, a synthetic organoselenium compound which inactivates hydroperoxides, exhibits anti-inflammatory activity *in vivo* and inhibits cholesterol uptake by a macrophage cell line. *Doni* (Padua, Italy) demonstrated that the increase of the extracellular antioxidant potential, brought about by the addition of synthetic antioxidants, interferes with the stimulus response coupling in blood platelets and inhibits platelet function upon a variety of stimuli. *Steiner* (Pawtucket, USA) summarized the antithrombotic potential of vitamin E, a natural antioxidant which also affects membrane fluidity and *Szczeklik* (Cracow, Poland) reported on a clinical trial which demonstrated that the daily administration of vitamin E to hyperlipidaemic subjects normalized their enhanced plasma lipid peroxide levels and increased serum antioxidant activity. Platelet aggregation, however, was hardly affected. Finally, *Arnout* (Leuven, Belgium) provided evidence that another natural antioxidant, uric acid, may be important in maintaining the prostacyclin producing potency of endothelium.

The second part of the Bad Ischl workshop was devoted to recent developments in other areas, related to lipids, eicosanoids and thrombosis. *Steiner* (Pawtucket, USA) reported on synthetic

phosphonolipids, one of which was able to modulate platelet aggregation because of its capacity to inhibit the release of arachidonic acid and its subsequent conversion into TxA_2 . Another phosphonolipid, moreover, appeared a specific inhibitor of platelet aggregation induced by PAF-Acether. Using diabetes mellitus as an example, *Cartwright* (Sheffield, England) discussed the inconsistencies with respect to the relationship between precursor availability, prostanoid production and platelet function *in vivo*. It was concluded that more detailed studies are required particularly with regard to the fatty acid composition of the various platelet phospholipid classes in disease states associated with an increased thrombotic tendency. The possible influence of low density lipoproteins on platelet aggregation may be one reason for the observed inconsistencies. Although "atherogenic" lipoproteins have repeatedly been demonstrated to induce platelet hypersensitivity, *Nimpf* (Graz, Austria) reported on extensive studies which did not show such an effect. To clarify this important issue, more research needs to be done.

Dietary lipids have always been an important topic of the subcommittee on lipids, prostanoids and thrombosis and new results were reported again during this meeting. The alleged beneficial effect of dietary fish(oil) in the prevention and treatment of ischaemic cardiovascular diseases, becomes ever more controversial. *Nordøy* (Tromsø, Norway) reported on a recent study which failed to demonstrate differences in cardiovascular mortality, platelet function, and serum lipids between two Norwegian populations with a high and low habitual fish intake. *Van Houwelingen* (Maastricht, the Netherlands) pointed out that many intervention studies with dietary fish(oil) were poorly designed. In a well-controlled trial she demonstrated the absolute necessity of a control group in this type of studies and of an objective method to check compliance. *Olsen* (Torshavn, Faroe Islands, Denmark) provided epidemiological evidence that a fish-enriched diet may be associated with prolongation of gestation and, consequently, with higher birth weights. He discussed the possible involvement of a diet-induced reduction of the formation of the 2-series prostanoids, resulting in a delayed onset of labour. Since thrombosis in the placental vessels has also been implicated in the

process of parturition, Olson's findings may also point to the antithrombotic potency of dietary fish. The mechanism(s) by which dietary fish(oil) exerts its putative antithrombotic effect may be based on a shift in the thromboxane-prostacyclin balance towards a less thrombogenic state. *Mest* (Halle, GDR) demonstrated that eicosa-pentaenoic acid, but not α -linolenic acid, prevents low density lipoproteins from inhibiting prostacyclin formation. Finally, attention was paid to dietary palm oil in relation to arterial thrombosis. Using a rat model, *Hornstra* (Maastricht, the Netherlands) demonstrated that palm oil, despite its high content of saturated fatty acids, lowers arterial thrombosis tendency which was associated with a decrease of the thromboxane-prostacyclin ratio measured in serum. Since palm oil becomes ever more important as an edible oil, more research is required as to its effects on the cardiovascular risk profile.

Extended abstracts of the papers presented at this meeting are published in this issue of Agents and Actions.

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