Role of Prostaglandins in Platelet Aggregation and Atherosclerosis

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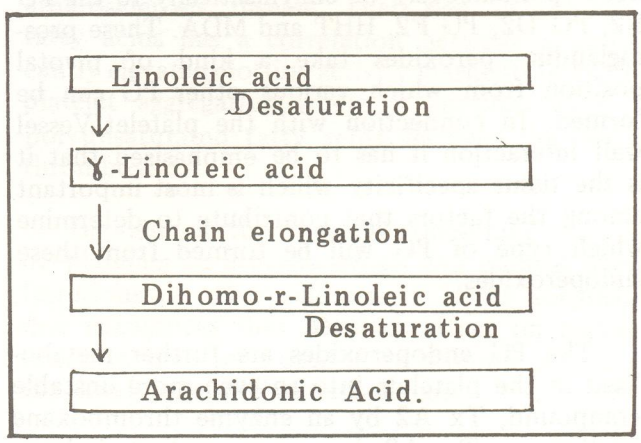
Atherosclerosis is one of the most common form of primary arteriopathy. It progresses insidiously and its damaging effects remain unknown for a long time before symptoms of cerebral, cardiac or peripheral ischaemia creates an imbalance between oxygen supply and demand of the tissues, with more or less severe luminal stenosis that may eventually be complicated by the formation of thrombi. It is influenced by numerous factors. Epidemiological investigations, especially studies of selected population groups with different biological profiles, demonstrate the harmful effects of certain hereditary or acquired disorders of lipid metabolism, diabetes, hypertension, cigarette smoking, emotional stress etc.

The term "atheroma" in ancient Greece was designated a cyst of Gruellike pus. In 1940 Marchand coined the term atherosclerosis to describe arteriosclerosis with simultaneous calcification of media. In 1940 Von Halter defined the yellow plaques in the arteries as "atheromas". The definition of atherosclerosis, as laid down by the WHO (1957) is purely morphological: "a variable combination of changes of the intima of arteries consisting of the focal accumulation tissue and calcium deposits, and associated with medical changes". At present, there is agreement that atherosclerosis is caused by Chronic injuries to the endothilium, which stimulate the proliferation of intimal smooth muscle cell, leads to accumulation of lipids in the cell, and in the long run, promote the formation of degenerative lesions rich in Cholesterol. Platelet aggregation at the site of the parietal lesion, stimulated by cellular growth factors, may play an important role in inducing intimal proliferation. Platelet function is regulated by the antagonistic effects of different Prostaglandins, like prostacyclin and thrombaxene A2, the balance action of which is influenced by certain alimentary polyunsaturated fatty acids. Reduced production of Prostacyclins in atherosclerotic lesions probably increase the thrombogenic and atherogenic efficacy of the platelets.

PROSTAGLANDINS:

Prostaglandins are essential fatty acids containing a 20-Carbon skeleton and consisting of a cyclopentane ring with two lateral chains. Depending on the degree of saturation of the side chains, a distinction is made among prostaglandins of the one, two and three series with one, two or three double bond respectively in the side chain. The prostaglandins of the two series are currently considered the most important in man. The classic prostaglandins of two series are PGE2, PGD2 and PGF2. The most recently discovered member of the family is called prostacyclin or PG12, which, as thromboxane A2 or Tx A2 differs slightly in its structure from that of the so called classic PG in the structure of the cyclopentane ring. Linoleic acid is the precursor of PG of the two series in the food. It undergoes transformation in the liver into arachidonic acid, which is the final substrate for the synthesis of the prostaglandins of two series.



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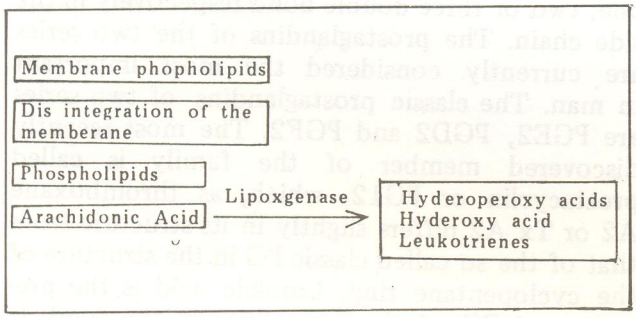
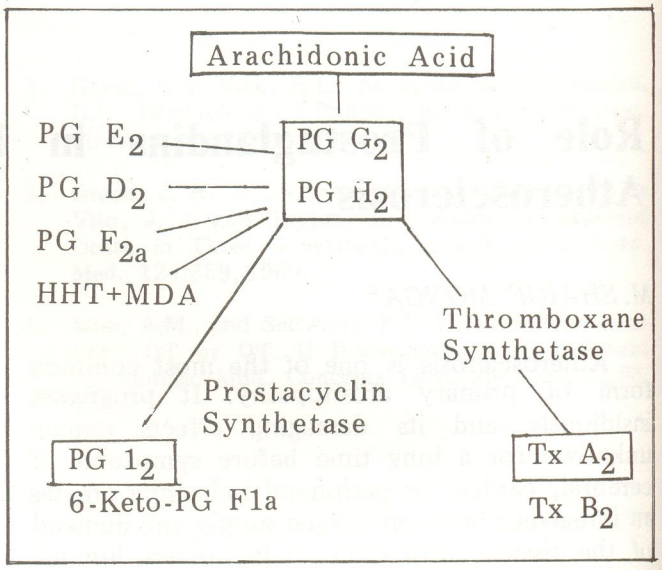
The main bulk of arachidonic Acid, derived from the linoleic acid or arachidonic acid in the food, is bound to plasma albumins and transported to different tissues where it is incorporated in mono-, di-, and triglycerides, cholesterol esters, and, above all, in the phospholipid fraction of the cell membranes. PG synthesis from arachidonic acid will occur only when it is available in the free acid form to serve as substrate. As soon as the integrity of the phospholipid bilayer in the membrance is disturbed by certain stimuli e.g. Mechanical (collision of a platelet with an endothilial cell can stimulate PG biosynthesis), Chemical (e.g. Neurotransmitters, mediactors of inflammations.), Hormonal (e.g. angiotension II, LH, TSH), or immunological stimuli (antigen-antibody reaction at the surface of sensitized cells), etc. Cellular phospholipids become available to phospholipases, which are able to liberate arachidonic acid. Once the arachidonic acid is free, it may serve as a substrate for two different enzyme systems, i.e. Cyclo-Oxygenase and lipoxygenase.



Cycloxygenase transforms arachidonic Acid into the prostaglandins endoperoxides PG G2 and PG H2, which are unstable and can be metabolized spontaneously or enzymsatically to the PG E2, PG D2, PG F2, HHT and MDA. These prostaglandin peroxides take a kind of pivotal position from which various other PG can be formed. In connection with the platelet/Vessel wall interaction it has to be emphasised that it is the tissue specificity which is most important among the factors that contribute to determine which type of PG will be formed from these endoperoxides.

The PG endoperoxides are further metabolised in the platelets into an even more unstable compound, Tx A2 by an enzyme thromboxane synthetase. Tx A2 is a very potent inducer



of platelet aggregation and a powerful constrictor of arterial smooth muscle cells. On the other hand, in the endothelial cells it is the prostacyclin synthetase which is mainly responsible for the transformation of endoperoxides into another labile substance, prostacyclin or PG 12, a vasodilator and inhibitor of platelet aggregation.

PROSTAGLANDINS AND PLATELET AGGREGATION.

The biochemical mechanisms by which Tx A2 activates platelet aggregation and by which prostacyclin inhibits this aggregation are largely based on an interactions with cyclic AMP formation. Tx A2 leads to a decrease in cyclic AMP in platelets and induces a release reaction from granules of ADP and serotonin which have aggregatory properties, hence an increase in the aggregation process. Prostacyclin on the other hand increases the cyclic AMP level in the thrombocytes; this rise in the cyclic AMP results in a decrease in the intracellular calcium which prevents the contents of the granules from being extruded and inbibits phospholipase activity and blocks the release of arachidonic acid.

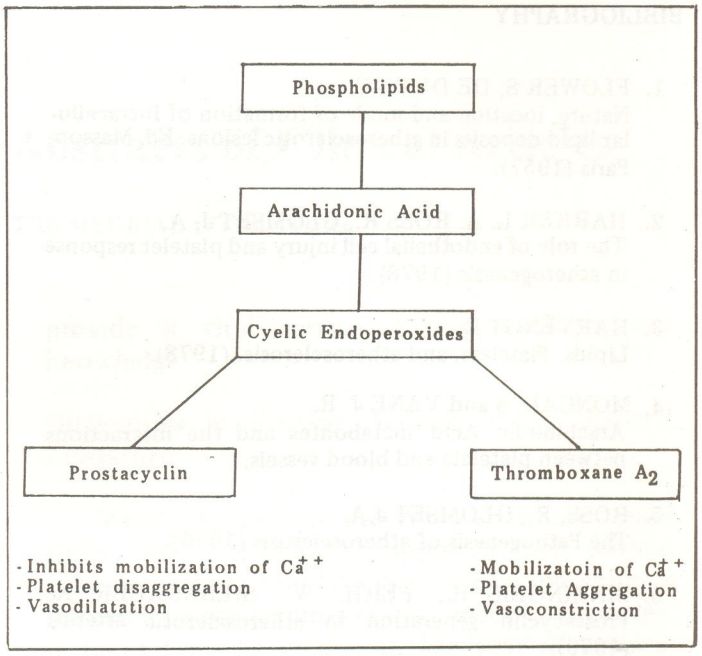
Platelet contact with the endothilial cells disturbs the integrity of the phospholipid bilayer in the two cells. Phospholipases release arachidonic Acid which is mainly transformed into Tx A2 in platelets whereas in endothilial cells it is almost exclusively metabolized into prostacyclin.

In intact endothilial cell prostacyclin activity predominates and the platelet is released into the blood stream. On the other hand injured endothelium, or accumulation of prostacyclin synthetase inhibitors, which can be found in atheromatus plaques, stimulate Tx A2 which results in platelet aggregation. However it has to be emphasied that the prostaglandinen-doperoxides-Tx A2-prostacyclin system is not the only mechanism involved in platelet aggregation, and that, depending on the type and intensity of the stimulus, other mediators such as ADP or platelet activating factor (PAF) may also come into play more or less markedly.

As it appears that platelets play an important role in atherogenesis, a normally intact endothilium protects itself by continuous production of prostacyclin, thereby preventing platelet from exerting their atherogenic action, therefore prostacyclin may be considered an "anti-atherosclerotic" hormone.

Platelet aggregation can be inhibited not only by the prostacyclin but also by a number of other substances the mode of action which is not necessarily linked to the metabolism of arachidonic Acid. There is evidence that the anti-aggregatory activity of these substances mainly consists in interfering with the production or degradation of cyclic AMP and/or the release of intracellular calcium.

In summary, the identification of the unstable arachidonic acid metabolites Tx A2 and PG 12 as the major products of the arachidonic acid cascade in the circulation has had a major effect on current concepts of thrombogenesis. Tx A2 which lowers platelet CAMP, induces platelet aggregation, and causes vasoconstriction, is opposed by PG 12 which elevates platelet cyclic AMP, inhibits platelet aggregation and causes vasodilation. It has been postulated that normal hemostasis represents a balance between platelet Tx A2 formation and vessel wall PG 12 production that theoretically could lead to thrombosis on one hand or bleeding on the other whenever an imbalance occurs. A corollary to this postulate implies that selective inhibition of thromboxane synthesis with maintenance of prostacyclin production may offer a new therapeutic approach to the prevention of thrombosis.



So far it has been shown that prostaglandins and platelets are of primary importance in the pathogenesis and the multiple clinical manifestations of atherosclerosis. Platelet function may also be important with the presence of predispensing factors for the development of complications of atherosclerosis in some congenital and acquired diseases.

Congenital Homocystinuria and type II hypercholesterolaemia are known to be associated with the development of premature atherosclerosis. Diabetes mellitus, Hypertension and Cigarette smoking also contribute to accelerated atherosclerosis disease. Diet rich in saturated fatty acids has a correlation between a significantly elevated clotting activity markedly increased platelet aggregation where as administration of polyunsaturated fatty acids decrease the risk of thrombosis.

In view of the findings concerning the role of platelets in atherosclerosis and clinical manifestations of atherosclerosis, it is not surprising that substances that have an effect on platelet function have been used in an attempt to inhibit the development of atherosclerosis.

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