A Rancid Culprit in Vascular Inflammation Acts on the Prostaglandin Receptor EP2

Norbert Leitinger

Although our knowledge about the mechanisms underlying atherosclerosis and its complications has dramatically increased, questions about the initiating factors of atherogenesis remain. Accumulating evidence suggests retention of low-density lipoprotein (LDL) particles in the subendothelial space with subsequent oxidative modification as key steps in atherogenesis. Oxidative modification initially gives rise to minimally oxidized LDL (MM-LDL), which was shown by Judy Berliner in 1990 to activate endothelial cells to specifically bind monocytes but not neutrophils. It was subsequently shown by the same group that the biological activity of MM-LDL primarily results from oxidation of phospholipids such as 1-palmitoyl-2-arachidonoyl-sn-3-glycero-phosphorylcholine (PAPC), yielding a series of structurally defined oxidation products (OxPAPC). The advances that have been made in dissecting the molecular components of MM-LDL responsible for its proatherogenic effect now allow for the experimental use of defined compounds rather than complex lipoproteins. One such biologically active oxidized phospholipid was structurally identified by Watson et al as 1-palmitoyl-2-epoxyisoprostane-sn-3-glycero-3-phosphorylcholine (PEIPC; Figure 1). Oxidized ("rancid") phospholipids were shown to accumulate in atherosclerotic lesions, and thus could be regarded as "culprits" in chronic inflammation. Although our knowledge about the mechanisms underlying atherosclerosis and its complications has dramatically increased, questions about the initiating factors of atherogenesis remain. Accumulating evidence suggests retention of low-density lipoprotein (LDL) particles in the subendothelial space with subsequent oxidative modification as key steps in atherogenesis. Oxidative modification initially gives rise to minimally oxidized LDL (MM-LDL), which was shown by Judy Berliner in 1990 to activate endothelial cells to specifically bind monocytes but not neutrophils. It was subsequently shown by the same group that the biological activity of MM-LDL primarily results from oxidation of phospholipids such as 1-palmitoyl-2-arachidonoyl-sn-3-glycero-phosphorylcholine (PAPC), yielding a series of structurally defined oxidation products (OxPAPC). The advances that have been made in dissecting the molecular components of MM-LDL responsible for its proatherogenic effect now allow for the experimental use of defined compounds rather than complex lipoproteins. One such biologically active oxidized phospholipid was structurally identified by Watson et al as 1-palmitoyl-2-epoxyisoprostane-sn-3-glycero-3-phosphorylcholine (PEIPC; Figure 1). Oxidized ("rancid") phospholipids were shown to accumulate in atherosclerotic lesions, and thus could be regarded as "culprits" in chronic inflammation. Although intracellular signaling pathways induced by various oxidized phospholipids had been studied, target receptors that are activated by these lipids remained unknown. Indications that oxidized phospholipids may act by binding to a G protein–coupled receptor (GPCR) came from studies by Parhami et al, who demonstrated that MM-LDL stimulates a putative Gαs-coupled receptor, increasing cyclic AMP (cAMP) levels in endothelial cells.

In this issue of Circulation Research, Li et al. demonstrate that the oxidized phospholipid PEIPC induces monocyte adhesion to endothelial cells by activating the prostaglandin E2 (PGE2) receptor EP2. Activation of EP2 by PEIPC increased cAMP levels, thus mimicking effects of an EP2-specific PGE2 analogue, butaprost. Furthermore, PEIPC was shown to activate PGE2 receptors in endothelial cells. The authors show that PEIPC competes with PGE2 for binding to EP2, and while PEIPC seems to be specific for EP2, PGE2 would also bind to EP1, 3, and 4. Activation of EP4 in macrophages stimulates antiinflammatory pathways via increasing cAMP levels, whereas in T-cells, for instance, EP4 can also stimulate proinflammatory cAMP-independent pathways. Consequently, the presence of both PGE2 and PEIPC would result in dual activation of EP2 and EP4 receptors in macrophages, likely potentiating anti-inflammatory effects. However, in other cell types the relative abundance of the two EP ligands may determine stimulation of individual receptor subtypes and thus the outcome of cell activation. Moreover, it is conceivable that specific activation of EP2 by PEIPC would buffer proinflammatory effects elicited by EP1 and EP3 receptor activation by PGE2.

The findings of the present study suggest that PEIPC–EP2 interactions may be important in vascular inflammation, and its pathophysiological relevance could be tested directly in vivo, for example in models of atherosclerosis. Future studies using mice deficient in EP2 and selective inhibitors should demonstrate whether PEIPC uses the EP2 receptor to induce vascular inflammation, and thus will affect the progression of atherosclerotic lesion formation. Moreover, because EP2 plays important roles not only in inflammation but also in blood pressure homeostasis and reproduction, as illustrated by genetic deletion of this receptor in mice, a role for
PEIPC in these settings seems possible and requires further investigation.

Another important aspect of the present study is the discovery of EP2 as a drugable target holding the potential to modulate inflammatory actions induced by oxidized phospholipids. Because both the prevention of their local formation and the selective destruction of biologically active oxidized phospholipids using antioxidants or enzymes, respectively, seem to be difficult undertakings, the discovery of a receptor that mediates the activity of one of these compounds opens new avenues for pharmacological intervention. Moreover, the activation of prostaglandin receptors by molecules that are free radical–derived makes this effect independent of COX. Therefore, the EP2 receptor may turn out to be an attractive pharmacological target in atherosclerosis and other inflammatory diseases.

The authors focused in their study on the EP2 receptor because it is expressed in endothelial cells and monocytes, important players in atherogenesis. However, the finding that PEIPC also activates the PGD$_2$ receptor DP may have important implications. In chronically inflamed tissue, where oxidized phospholipids accumulate, activation of cells bearing the DP receptor may occur by PEIPC, even in the absence of COX-derived prostaglandin production, and result in modulation of the inflammatory response. For instance, cell types that are activated via the DP receptor include bronchial epithelial cells, implying a role for PEIPC-DP interactions in settings of lung inflammation and asthma.

What are the structural implications for oxidized phospholipid (PEIPC)-receptor (EP2) interactions? E-ring isoprostanes were shown to be recognized by the thromboxane receptor (TP), but also EP receptors; however, structural requirements for individual receptor subtype recognition have not been elucidated yet. The epoxyisoprostane in PEIPC contains an E-prostane ring; however, the structural motif conferring specificity for the EP2 receptor is not known. Whether the epoxide in PEIPC plays a role in specific receptor recognition remains to be shown. Another structural question to be answered is whether PEIPC is recognized by EP2 as an intact phospholipid, or whether the epoxyisoprostane moiety needs to be hydrolyzed by a phospholipase A$_2$ (PLA$_2$). The latter would imply a role for secretory PLA$_2$s, which recently had been attributed important roles in atherogenesis. Even if the intact epoxyisoprostane phospholipid is recognized by EP2, hydrolysis by PLA$_2$ might increase binding affinity. On the other hand, it was demonstrated previously that PLA$_2$ treatment of PEIPC resulted in loss of biological activity. In any case, it remains to be shown for which sPLA$_2$ subtype PEIPC would be a good substrate. Whatever the structural requirements for receptor recognition are, oxidation products of phosphatidylserine, phosphatidylcholine, and phosphatidylethanolamine contain homologous functional groups that result in similar biological activities. Thus, epoxyisoprostanes that are recognized by EP2 are potentially formed from all kinds of arachidonate-containing phospholipids, indicating accumulation of quite significant amounts of these biologically active compounds in inflamed tissue.

By screening a substantial number of candidate GPCRs, the authors excluded various other known phospholipid as...
well as orphan receptors as mediators for oxidized phospholipid-induced cAMP-dependent monocyte adhesion. The finding that other biologically active oxidized phospholipids that are present in OxPAPC act neither on EP nor on the other investigated candidate receptors, including the PAF receptor and lysophospholipid receptors, implies the presence of as of yet unidentified receptors. Together, the identification of the prostaglandin E2 receptor EP2 as a receptor for the oxidized phospholipid PEIPC provides new insights into the mechanisms by which monocytes are selectively recruited to chronically inflamed tissue and should ultimately lead to the development of novel therapeutic approaches against chronic inflammatory diseases such as atherosclerosis.

Acknowledgments

This work was supported by a Partner’s Fund Award of the Robert M. Berne Cardiovascular Research Center and a Research and Development Grant from the University of Virginia. The author thanks Dr Alexandra Kadl for artwork and valuable discussions.

References


Keywords: oxidized phospholipids ■ prostaglandin receptors ■ atherosclerosis ■ endothelial cells ■ monocytes ■ inflammation
A Rancid Culprit in Vascular Inflammation Acts on the Prostaglandin Receptor EP2
Norbert Leitinger

Circ Res. 2006;98:587-589
doi: 10.1161/01.RES.0000215626.34470.e6
Circulation Research is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2006 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7330. Online ISSN: 1524-4571

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circres.ahajournals.org/content/98/5/587

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Circulation Research can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Circulation Research is online at:
http://circres.ahajournals.org//subscriptions/