Editorial

Novel Antioxidant Action of Aspirin May Contribute to Its Beneficial Cardiovascular Actions

Michael S. Wolin

In this issue of Circulation Research, Oberle et al report a novel action of therapeutic doses of aspirin that may play a prominent role in the cardiovascular protective effects of this important drug. Investigation of an initial preliminary observation that aspirin protected cultured endothelial cells against oxidative stress elicited by exposure to hydrogen peroxide resulted in evidence that it appears to function through increasing the expression of the cellular iron–binding protein ferritin. As discussed in the article by Oberle et al, evidence is emerging from clinical studies that increased cellular iron levels appear to be a risk factor in coronary artery disease. It is thought that iron can become an important contributor to enhancing the injury caused by oxidative stress as it is released from binding sites in cellular systems that normally use it for other catalytic or regulatory roles. Ferritin seems to bind iron in a manner which inhibits its ability to participate in oxidant injury. Thus, ferritin can be viewed as being a protective cellular antioxidant. When aspirin causes the elevation of ferritin, it is functioning in a manner which should reduce the tissue injury caused by oxidant stress.

Based on the data of Oberle et al, previously identified actions of aspirin as an inhibitor of the biosynthesis of prostaglandins or as a scavenger of reactive radicals through its conversion to salicylic acid do not appear to contribute to the observed effects of aspirin on ferritin expression. In this study, the iron chelator desferrioxamine prevented the effects of aspirin on the expression of ferritin, and this suggested to the authors that aspirin may be interacting with the iron-responsive activation of the translation of ferritin. Much of our knowledge of the ferritin system centers on its importance in the cellular control of iron levels and the storage of iron in a relatively inert form. It has been known for over a century that iron in its ferrous (Fe²⁺) oxidation state markedly enhances the reactivity of peroxides. A large component of the literature on reactive O₂ species is devoted to documenting the many facets of the destructive actions of hydroxyl radical and oxidized iron species with hydroxyl radical–like properties which are produced by the reaction of peroxides with different forms of chelated Fe²⁺. More recently, it has been realized that superoxide anion, nitric oxide, and their derived species can contribute to the release of iron. However, observations reported in the literature document both stimulatory and inhibitory effects of reactive O₂ and N₂ species on the expression of ferritin. It has been observed that oxidants, including peroxynitrite, increase the expression of ferritin, whereas nitric oxide has been observed to decrease the expression of ferritin through mimicking the effect of low iron on the iron-responsive element-binding protein. This action of nitric oxide has been observed to be associated with an initial protective effect against oxidative injury, potentially mediated through a depletion of cellular iron, and over time an enhanced susceptibility to injury as a result of decreased levels of ferritin. Thus, there is much evidence to support the idea that ferritin functions as an antioxidant by reducing the reactivity of iron. However, we have only a limited understanding of how cellular redox processes control the expression of ferritin under conditions which are relevant to cardiovascular pathophysiology. If future studies determine that aspirin increases endothelial cell ferritin levels in vivo, it is likely that this mechanism will be considered an important component of its protective cardiovascular actions.

It is possible that modulation of the expression of ferritin by aspirin could activate additional regulatory processes as a result of altering the potential influence of iron on oxidant-mediated signaling mechanisms. For example, peroxides appear to activate regulatory processes such as the stimulation of prostaglandin production, soluble guanylate cyclase activity, and other mechanisms as a result of their interaction with peroxide metabolizing enzymes. An increase in cellular levels of iron is likely to shift the actions of peroxides to additional signaling mechanisms or pathophysiological processes, and the level of activation of these mechanisms is likely to be controlled by the expression of ferritin and its effect on the availability of iron. As previously emphasized, it is well established that the availability of iron enhances the injury-producing effects of peroxides through generating hydroxyl radical–like species. There is also a significant amount of evidence suggesting that these species may activate vascular signaling mechanisms. However, the actual processes involved in hydroxyl radical–like oxidant interactions with cellular control systems are generally poorly understood. Many aspects of the chemical reactions through which iron-catalyzed hydroxyl radical–like species cause tissue injury have been identified in studies on lipid peroxidation, protein modification, and cellular injury. It is possible that some of these hydroxyl radical–related actions activate signaling mechanisms at low levels of oxidant stress. For
example, many of the poorly understood pathways of oxidant signaling have key regulatory components whose activity is controlled by the redox status of thiol groups. It is likely that reactive species derived from iron-peroxide interactions may selectively modify thiols on some of these oxidant-regulated systems. Although it is conceivable that iron has important roles in pathophysiological signaling processes involving oxidants, we currently have but a limited understanding of the fundamental mechanisms involved. Thus, it can be hypothesized that when aspirin increases the levels of ferritin, it is likely to attenuate the activation of both injury and pathophysiological signaling mechanisms associated with the development of vascular disease.

The relative importance of the enhancement of the expression of ferritin by aspirin in the cardiovascular protective effects of this drug compared with other well-established mechanisms, such as the inhibition of prostaglandin synthesis, is not known. There is considerable evidence that oxidant signaling events are major contributors to the cardiovascular pathophysiology of unstable angina, myocardial infarction, and sudden death. If aspirin is observed in future clinical studies to increase tissue levels of ferritin, it could be one of the most readily available pharmacological or dietary methods of enhancing the function of this important antioxidant system. Although dietary antioxidants have been observed to produce modest protective effects in human cardiovascular diseases, it is possible that enhancing endogenous enzymatic antioxidant systems could produce even greater levels of protection against pathological processes mediated through oxidant stress.

References

Key Words: aspirin ■ ferritin ■ endothelial cell ■ gene expression ■ antioxidant defense mechanism
Novel Antioxidant Action of Aspirin May Contribute to Its Beneficial Cardiovascular Actions
Michael S. Wolin

Circ Res. 1998;82:1021-1022
doi: 10.1161/01.RES.82.9.1021
Circulation Research is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1998 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/82/9/1021

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/