Excitement of Clinical Investigation
New Basic Mechanisms of Action After Drug Introduction

Edward D. Frohlich

Enormous personal satisfaction is frequently derived from experiences resulting from systematic clinical investigation. Such are the lessons that have been learned from the tremendous insight that has evolved concerning the careful clinical and fundamental study of new therapeutic agents, events after their release for general clinical use. This has been the case derived from exciting gains into the cardiac and vascular remodeling after introduction of the angiotensin-converting enzyme inhibitors and the statins.

According to the editors, an editorial commentary is intended to “highlight, provide a further perspective, and enhance the overall significance of a study that is novel, timely, and contributes to our understanding of the physiology, pathophysiology, clinical treatment or prevention of hypertension.”

To my way of thinking, there is no better example of such an article to fulfill these criteria than “Modulation of Angiotensin II–Mediated Hypertension and Cardiac Remodeling by Lectin-Like, Oxidized Low-Density Lipoprotein Receptor-1 Deletion” by Hu et al. Inherent in this commentary are its key words: angiotensin II, cardiac remodeling, and lectin-like, oxidized low-density lipoprotein receptor-1 (LOX-1) deletion. Moreover, central to its thesis are the concept and mechanisms of cardiovascular “remodeling.”

The role of angiotensin in cardiac remodeling was first introduced into pathophysiology, clinical treatment, and prevention by Marc A. and Janice M. Pfeffer in 1988 after a discussion (which I witnessed) with Eugene Braunwald. That conversation concerned submission of an abstract on the benefits of prolonged survival with long-term captopril therapy of rats with myocardial infarction and heart failure for consideration at the forthcoming annual scientific meeting of the American Heart Association. At that time, Braunwald suggested the need for a “hook” so that the article could be accepted on the “main arena” of the program rather than at a smaller session. He thereupon suggested the term “remodeling.” That abstract was accepted on that year’s “arena session,” and I suggest that we have all been hooked on that term ever since. Their laboratory findings were subsequently confirmed clinically in a mechanistic trial of cardiac enlargement after myocardial infarction. The translation of the concept and fundamental work demonstrating inhibition of ventricular remodeling to improve prognosis was then demonstrated in the multicenter clinical Survival and Ventricular Enlargement Trial; and it was subsequently confirmed by a number of trials bearing a host of acronyms. Each of these trials demonstrated the following: inhibition of the renin-angiotensin system prevented remodeling of the left ventricle, subsequent development of left ventricular failure, a second myocardial infarction, high-grade arrhythmias, and death. I am personally thrilled by this anecdotal story, because the initial experimental investigations were the substance of the late Janice Pfeffer’s graduate thesis conducted in my laboratory in Oklahoma (unpublished communication, 1976).

Subsequent studies demonstrated remodeling of large arteries and arterioles in hypertension not only with angiotensin-converting enzyme inhibitors but also with other classes of angiotensin-inhibiting pharmacological agents. The vascular and ventricular remodeling process was later shown to have been influenced by the mitogenic effects of angiotensin II in the fibromyocytic synthesis of collagen and fibrosis of the ventricular or vascular walls. This ensuing fibrosis, thus, promoted restructuring of the ventricle by dilatation, inefficiency of contractility, and, subsequently, failure.

Not only are angiotensin II–inhibiting agents of great value in treating and preventing the adverse pathophysiological events associated with hypertension and its consequences on its target organs, but another class of cardiovascular agents, the “statins,” have also been exceedingly useful in treating hyperlipidemias and for the inhibition of atherosclerosis. Recent laboratory studies have demonstrated that the statins seem to have pleiotropic biological effects. These actions involve the low-density lipoprotein receptors of the ventricles and arterioles and account for their important role in treating hyperlipidemia and atherosclerosis, as well as mediating other events.

In this regard, a series of studies was begun in Mehta’s laboratory that demonstrated that angiotensin II initiated yet another mechanism for producing oxidative stress. Thus, with angiotensin II type 1 receptor stimulation there is expression of a LOX-1. LOX-1 can, in turn, upregulate expression of angiotensin II type 1 receptor so that activation of both receptors, individually and apparently with receptor crosstalk, induces a state of oxidative stress that also promotes remodeling by permitting fibromyocytic stimulation of collagen synthesis. In their current work, the team used LOX-1 knockout mice to determine whether their hypothesis was correct and that this enzyme was found to be responsible for the adverse consequences of angiotensin II infusion in these animals. Their findings, therefore, provide strong evidence that LOX-1 was a major mediator in the development of hypertension and the angiotensin II–induced
events of oxidative stress, myocardial and vascular collagen synthesis, and, consequently, the negative effect of cardiac remodeling.

These 2 lines of investigation involved postmarketing investigation of 2 major cardiovascular agents introduced for different clinical indications. They underscore the importance of returning to the laboratory from the “bedside” and then back to the bedside to learn further vital information on yet other actions that may provide new knowledge that may promote the potential reduction of events that account for increased cardiovascular morbidity and mortality. To this end, we now learn that the consequences of angiotensin II actions mediated through angiotensin-converting enzyme inhibition involve the LOX-1 receptor. Thus, we now learn that LOX-1 receptor action provides at least one explanation for the mechanisms that account for the action of angiotensin II to elevate arterial pressure and promote oxidative stress, cardiovascular collagen synthesis, and ventricular and vascular fibrosis and remodeling. What a beautiful elucidation of the concept of Claude Bernard and that of his described scientific method!

Disclosures
None.

References


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Hypertension. 2008;52:465-466; originally published online July 21, 2008;
doi: 10.1161/HYPERTENSIONAHA.108.116558
Hypertension is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0194-911X. Online ISSN: 1524-4563

The online version of this article, along with updated information and services, is located on the
World Wide Web at:
http://hyper.ahajournals.org/content/52/3/465

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