Hypothesis

Transcription-Modulating Drugs
A New Frontier in the Treatment of Essential Hypertension

Theodore W. Kurtz, David G. Gardner

Abstract—While the promises of gene therapy may be years away from realization, the therapeutic use of drugs that act by modifying gene transcription is a well-established practice in clinical medicine. Although transcription-modulating drugs are frequently used in many different specialties, the deliberate development and use of these agents in cardiovascular medicine has been comparatively limited. However, research advances in the area of gene transcription and in the molecular genetic regulation of blood pressure, insulin resistance, lipid metabolism, and cell growth are providing new opportunities for controlling the expression of genes that are relevant to the pathogenesis of cardiovascular disease and essential hypertension. These research advances are beginning to converge in the development of transcription-modulating drugs with the potential to attack genetically determined risk factors that often cluster in patients with essential hypertension. Ligand-activated transcription factors that serve as receptors for small lipophilic compounds such as the thiazolidinediones and retinoids represent examples of potential therapeutic targets with direct effects on the expression of genes relevant to the pathogenesis of essential hypertension and its complications. Mounting evidence suggesting that the superior cardiorenal protective properties of converting enzyme inhibitors are related in part to their ability to indirectly modify the expression of genes in the heart and vasculature provides provisional support for the clinical value of this therapeutic approach. Given the success of transcription-modulating drugs in the treatment of type II diabetes and many other clinical disorders, it is anticipated that these agents will be developed as tools for the prevention and treatment of hypertension and cardiovascular disease in the not too distant future. (Hypertension. 1998;32:380-386.)

Key Words: hypertension, essential ■ genetics ■ thiazolidinediones ■ transcription ■ drugs ■ blood pressure ■ angiotensin

It is my hope that hypertension and atherosclerosis will be considered as a new class of diseases—diseases of regulation. Irvine H. Page, 1967

Over the past several decades, it has become increasingly recognized that essential hypertension, or at least a major subset of essential hypertension, is a genetically complex metabolic and cardiovascular disorder that involves altered regulation of blood pressure, insulin sensitivity, lipid metabolism, and vascular growth and function. A substantial research effort has been launched in an attempt to identify the genetic factors that contribute to this clustering of risk factors in patients with essential hypertension. Pharmaceutical companies now emphasize that their antihypertensive drugs not only reduce blood pressure but also ameliorate, or at least do not exacerbate, insulin resistance and dyslipidemia. Indeed, with respect to the modern-day treatment of high blood pressure in patients with essential hypertension, the popular refrain seems to be “It’s not just how low you make it, but how you make it low.” Yet the reality is that most of the antihypertensive agents in use today were designed primarily to lower blood pressure, not to treat a genetically complex syndrome in which hypertension is but one element.

Although the multigenic nature of essential hypertension is widely accepted, cardiovascular pharmacologists have tended to focus their therapeutic efforts on the selective manipulation of proteins associated with individual blood pressure control pathways and have not attempted to attack this complex syndrome at the molecular genetic level. Pharmacological strategies that target multiple risk factors at the genetic level might well be anticipated to afford greater cardiovascular protection than those which target an individual protein that controls a single step, or at best a few steps, in the pathways that regulate blood pressure. In addition, therapy directed at gene expression might be expected to be particularly effective in counteracting those chronic sequelae (eg, hypertrophy in the vascular wall or myocardium) that have the most significant impact on the morbidity and mortality of the disease. Admittedly, it will be many years before investigators define all of the primary genetic factors that underlie the pathogenesis of cardiovascular disease in patients with essential hypertension. However, it is not too early to begin considering pharmacological strategies for manipulating the expression of genes that influence known cardiovascular risk factors in this disorder. Accordingly, in this article, we consider the
TABLE 1. Examples of Commonly Used Drugs That Act by Modulating Gene Expression

<table>
<thead>
<tr>
<th>Examples</th>
<th>Targets</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hydrocortisone</td>
<td>Glucocorticoid receptors</td>
</tr>
<tr>
<td>All-trans retinoic acid</td>
<td>Retinoic acid receptors</td>
</tr>
<tr>
<td>Calcitriol</td>
<td>Vitamin D receptors</td>
</tr>
<tr>
<td>Levothyroxine</td>
<td>Thyroid hormone receptors</td>
</tr>
<tr>
<td>Flutamide</td>
<td>Androgen receptors</td>
</tr>
<tr>
<td>Estradiol, tamoxifen, raloxifene</td>
<td>Estrogen receptors</td>
</tr>
<tr>
<td>Spironolactone</td>
<td>Mineralocorticoid receptors</td>
</tr>
<tr>
<td>Troglitazone</td>
<td>Peroxisome proliferator–activated receptors</td>
</tr>
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</table>

special therapeutic potential of transcription-modulating drugs for the management of essential hypertension. We discuss ligands for nuclear hormone receptors and the converting enzyme inhibitors as two distinctly different classes of transcription-modulating drugs to illustrate just a few of the ways in which gene expression might be modified for therapeutic purposes in patients with essential hypertension.

Transcription-Modulating Drugs: Controlling Gene Expression for Therapeutic Purposes

Whereas medical treatments based on the controlled delivery of nucleic acid sequences (gene therapies) appear to be a long way off, medical treatments based on regulation of the expression of multiple genes have been approved for some time in many fields, including endocrinology, rheumatology, dermatology, and oncology (Table 1). In contrast, the deliberate use of transcription-modulating drugs in cardiovascular medicine has been surprisingly limited. Although estradiol represents a well-known example of a transcription-modulating drug with cardioprotective properties, its wide range of clinical effects, including the potential for carcinogenesis and its undesirable effects in the male population, tend to limit interest in the use of estradiol for the treatment of specific cardiovascular disorders. However, on the basis of steady advances in research on fundamental aspects of gene regulation, as well as on new methods for high-throughput drug screening, pharmaceutical companies are destined to develop more potent and specific compounds that influence the expression of genes relevant to the pathogenesis of cardiovascular disease. The selective estrogen receptor ligand raloxifene provides an example of a transcription-modulating drug with improved clinical specificity over first-generation estrogen receptor ligands.

Transcription-Modulating Drugs and Treatment of Essential Hypertension as a Complex Genetic Disorder: Which Targets?

In linkage studies in humans and in spontaneously hypertensive rats, it has recently been found that quantitative trait loci influencing blood pressure, lipid metabolism, insulin action, and susceptibility to hypertension-induced vascular injury may cluster within certain chromosome regions. This raises the possibility that the coinheritance of multiple cardiovascular risk factors may be determined in part by linked genes or even the same genes. Certainly, if individual genes are identified that exert pleiotropic effects on blood pressure, lipid metabolism, insulin action, and perhaps cardiovascular cell growth, it will not be difficult to imagine how the controlled expression of such genes might be useful in the management of essential hypertension. However, even without invoking “unified genetic field theories” to explain the clustering of cardiovascular risk factors in patients with essential hypertension, one can still entertain the concept of manipulating gene function for the purpose of treating the syndrome. That is, for transcription-modulating drugs to be useful in the treatment of essential hypertension, they need not modify the expression of the primary genes responsible for the inherited transmission of the disorder. As illustrated by the thiazolidinediones and other nuclear receptor ligands discussed below, one can envision the development of multifunctional therapeutic agents that attack genes regulating insulin resistance, dyslipidemia, vascular growth, and hypertension without accepting the notion that a primary genetic disturbance in carbohydrate metabolism underlies the syndrome of essential hypertension.

Thiazolidinediones as Transcription-Modulating Drugs Relevant to Essential Hypertension and Cardiovascular Disease

The thiazolidinediones represent a class of transcription-modulating drugs that exert effects on blood pressure, carbohydrate and lipid metabolism, and vascular growth and function. Until recently, the thiazolidinediones have been viewed primarily as insulin-sensitizing compounds that serve to improve glucose tolerance and decrease hepatic glucose output. However, it is now recognized that thiazolidinediones also have beneficial effects on lipid metabolism and cardiovascular function (Table 2). Troglitazone is a thiazolidinedione that was recently approved for the treatment of type II diabetes. In nondiabetic as well as in diabetic humans and animals, thiazolidinediones such as troglitazone have been shown to ameliorate insulin resistance, reduce circulating lipids and fatty acids, and decrease blood pressure. The effects of these agents on insulin resistance have been shown to be clinically significant, whereas the magnitude of their effects on lipid metabolism and blood pressure remains to be clearly defined. As more potent thiazolidinediones are developed and tested, their potential clinical effects on multiple cardiovascular risk factors should become evident. The fact that a first-generation thiazolidinedione of only moderate potency can reduce blood pressure in normotensive subjects strongly suggests that these agents will be capable of decreasing blood pressure in patients with essential hypertension.
Addition, PPAR response elements, which are located in a variety of genes. In degree of variability can be tolerated in the sequence of the contain peroxisome proliferator response elements (PPRE). A heterodimers in turn modulate the transcription of genes that would appear to have greater potential for preventing the modulating drugs that target clusters of genetic risk factors 

Thiazolidinediones have also been shown to block growth factor–induced increases in the proliferation of human coronary artery smooth muscle cells, inhibit smooth muscle cell migration, and attenuate restenosis in animal models of balloon-catheter vascular injury. Clearly, transcription-modulating drugs that target clusters of genetic risk factors would appear to have greater potential for preventing the cardiovascular complications of essential hypertension than drugs that are designed primarily to lower blood pressure.

**Figure 1.** Schematic representation shows how small lipophilic molecules enter the cell and activate intranuclear receptors that modulate gene transcription. In this example, the thiazolidinedione troglitazone is shown entering the nucleus, where it activates heterodimers of PPARγ and RXR. The ligand-activated heterodimers in turn modulate the transcription of genes that contain peroxisome proliferator response elements (PPRE). A degree of variability can be tolerated in the sequence of the response elements, which are located in a variety of genes. In addition, PPARγ-RXR heterodimers can be activated by ligands for RXR (retinoids) as well as by ligands for PPARγ. LBD indicates ligand-binding domain of the intracellular receptor; DBD, DNA-binding domain of the intracellular receptor. The solid triangle represents a ligand for PPARγ; solid oval, a ligand for RXR.

**Figure 2.** A, Schematic representation shows how various repressor proteins inhibit transcription by limiting accessibility of the core transcription machinery (CTM) to DNA sequences within the histone-shielded chromatin. In the absence of activating ligands, the PPARγ-RXR heterodimers do not stimulate the transcription of genes containing target peroxisome proliferator response elements (PPRE) (shown here as a hexameric repeat of TGACCT separated by a single base). B, On activation of PPARγ-RXR heterodimers by ligands for either PPARγ or RXR, activator proteins are recruited and/or repressor proteins displaced, which in turn promotes histone acetylation and enables the CTM to access the DNA and modulate the expression of genes containing the appropriate response elements. LBD indicates ligand-binding domain of the intracellular receptor; DBD, DNA-binding domain of the intracellular receptor.

**Ligand-Activated Transcription Factors and the Mechanism of Action of Thiazolidinediones**

The multifunctional actions of thiazolidinediones stem largely from their primary effects on the transcription of genes involved in the control of glucose and lipid metabolism, vascular function, and cell growth. How do thiazolidinediones influence the expression of multiple genes? The endogenous receptor for the thiazolidinediones is the peroxisome proliferator–activated receptor-γ (PPARγ), a member of the class II family of nuclear hormone receptors (Figure 1). Nuclear receptors like PPARγ possess DNA binding domains that recognize specific DNA sequences (response elements) located in the regulatory regions of their target genes (Figure 1). Binding of thiazolidinediones to PPARγ causes receptor activation that in turn induces changes in the transcriptional activity of genes that contain peroxisome proliferator response elements (Figure 1). Parenthetically, the term “peroxisome proliferator–activated receptor” is a misnomer with respect to PPARγ because PPARγ, unlike PPARα (the first PPAR subtype that was identified), is not activated by chemicals that induce proliferation of peroxisomes.

The precise mechanisms whereby ligand activation of nuclear receptors leads to changes in gene expression are not fully understood. However, it appears that ligand-induced alterations in receptor conformation may attract or repel key cofactors that influence histone acetylation, modify chromatin structure, and regulate access of the core transcriptional machinery to target gene sequences (Figure 2). It also should be noted that for PPARγ to be functionally active, it must partner with the retinoid X receptor (RXR) (Figures 1 and 2). Furthermore, PPAR-RXR heterodimers can be activated by ligands for RXR as well as by ligands for PPARγ. This may explain why ligands for RXR (“retinoids”) exhibit some of the same insulin-sensitizing properties as ligands for PPARγ and raises the possibility that retinoid derivatives may also be capable of modifying the assortment of cardiovascular risk factors observed in patients with essential hypertension. A recent study from Miano et al indicated that all-trans retinoic acid is capable of suppressing platelet-derived growth factor (PDGF)–stimulated mitogenesis in cultured vascular smooth muscle cells, lending further support to this hypothesis. Retinoids have already found clinical utility in the management of promyelocytic leukemia and hyperproliferative disorders of the epidermis. Thus, clinical experience with these agents already exists that might be extrapolated to the cardiovascular paradigm discussed here.

Although the full spectrum of genes that can be regulated by PPARγ remains to be defined, DNA response elements for PPARγ have been found in the promoter regions of a variety of genes, including a number involved in lipid and fatty acid metabolism. Thus, the hypolipidemic effects of troglitazone appear to involve changes in the expression of genes that inhibit lipolysis and promote lipogenesis. The insulin-sensitizing effects of thiazolidinediones may be secondary to
reductions in fatty acid levels as well as to changes in the transcriptional activity of genes that are primarily or secondarily involved in insulin action and/or glucose transport.\textsuperscript{24,32,33} In addition, a recent study by Adams and colleagues\textsuperscript{34} suggests that thiazolidinediones may favor the accumulation of lipid in subcutaneous fat rather than visceral fat, an effect that may be of particular benefit in patients with insulin resistance and hypertension. The antihypertensive effects of troglitazone and other thiazolidinediones are likely to involve multiple mechanisms, including improved insulin sensitivity, changes in fatty acid levels, changes in the production of vasodilators or vasoconstrictors, blockade of L-type calcium channels, and direct effects on the vasculature.\textsuperscript{13,14,17,35–39} Finally, the antiproliferative effects of thiazolidinediones appear to involve effects on MAP kinase, serine-threonine phosphatase PP2A, and key transcriptional events that regulate cell cycle progression.\textsuperscript{18,20,40}

**Vitamin D–Dependent Regulation of Gene Expression in the Cardiovascular System**

PPARY and retinoic acid (RAR)/RXR are not the only members of the nuclear receptor family that can regulate the expression of genes relevant to hypertension and cardiovascular disease. The liganded vitamin D receptor (VDR) has also been demonstrated to possess growth-inhibitory activity in vascular smooth muscle and cardiac myocytes. Weishaar and Simpson\textsuperscript{41} showed that induction of vitamin D deficiency in rats led to elevations in blood pressure and cardiac hypertrophy. Correction of the attendant hypocalcemia, without restoration of vitamin D levels, led to a reduction in blood pressure but did not correct the hypertrophy. Other studies have documented vitamin D–dependent antimitogenic activity in vascular smooth muscle and cardiac myocytes. Weishaar and Simpson\textsuperscript{41} showed that induction of vitamin D deficiency in rats led to elevations in blood pressure and cardiac hypertrophy. Correction of the attendant hypocalcemia, without restoration of vitamin D levels, led to a reduction in blood pressure but did not correct the hypertrophy. Other studies have documented vitamin D–dependent antimitogenic activity in vascular smooth muscle and cardiac myocytes.\textsuperscript{41,44} The latter is VDR- and ligand-dependent. Interestingly, the nonhypercalcemic analogues of vitamin D share this growth suppressant activity in vitro,\textsuperscript{41} underscoring the potential utility of this approach in treating disorders typified by undesirable growth responses in the cardiovascular system.

**ACE Inhibitors as Examples of Transcription-Modulating Drugs Relevant to Essential Hypertension and Cardiovascular Disease**

Angiotensin-converting enzyme (ACE) inhibitors are not typically classified as transcription-modulating drugs and were certainly not designed to address essential hypertension at the level of the nucleus. However, there is mounting evidence that angiotensin II (Ang II) can affect the transcription of multiple genes related to cell growth and proliferation, atherogenesis, thrombus formation, etc.\textsuperscript{45–52} These observations, together with the apparently superior cardioprotective properties of ACE inhibitors, suggest that it may prove instructive to consider these agents from a gene-regulation perspective. Ang II has been shown to induce the expression of multiple genes, including proto-oncogenes, growth factor genes, genes of the fibrinolytic system, genes involved in aldosterone biosynthesis, extracellular matrix genes, and hypertrophic marker genes (Table 3).\textsuperscript{45–54} Because pharmacological blockade of the renin-angiotensin system can inhibit changes in gene expression otherwise induced by Ang II, ACE inhibitors may be indirectly viewed as transcription-modulating drugs. While the ability of ACE inhibitors to modify gene expression may also involve changes in levels of bradykinin or other peptides, many if not most of their transcriptional effects stem from reductions in Ang II and are shared by the angiotensin receptor blockers.

**Angiotensin Signaling Mechanisms and Gene Transcription**

Although an in-depth review of the mechanisms underlying Ang II effects on gene transcription is beyond the scope of this article, some recent advances in the field merit particular attention. The ability of Ang II to induce changes in gene expression begins with angiotensin receptor binding and subsequent activation of a variety of intracellular kinases. These intracellular kinases ultimately entrain the phosphorylation and activation of intracytoplasmic and intranuclear proteins that bind to specific DNA response elements and modify the expression of a host of key genes involved in cell growth, proliferation, and function (Figure 3). For example, Ang II has been shown to activate the extracellular signal–regulated protein kinase(s) (ERKs).\textsuperscript{55,56} Such activation subsequently leads to phosphorylation of Elk, a protein that is involved in assembly of the ternary complex on the serum

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**TABLE 3. Examples of Genes That Can Be Regulated by Ang II**

<table>
<thead>
<tr>
<th>Type</th>
<th>Early genes/proto-oncogenes</th>
<th>Growth factor genes</th>
<th>Cell matrix factor genes</th>
<th>Hypertrophic marker genes</th>
<th>Fibrinolytic system genes</th>
<th>Miscellaneous genes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Examples</td>
<td>fos, myc, myb, jun, jun-B, egr-1</td>
<td>Transforming growth factor-β1, PDGF-A chain, fibroblast growth factor-2, insulin-like growth factor-1, insulin-like growth factor-1 receptor</td>
<td>Fibronectin, collagen type I-α1, collagen type III-α1, laminin-β1, laminin-β2</td>
<td>Atrial natriuretic peptide, brain natriuretic peptide, skeletal muscle actin-α1</td>
<td>Plasminogen activator inhibitor, types 1 and 2</td>
<td>Aldosterone synthase (CYP11B2), endothelial nitric oxide synthase</td>
</tr>
</tbody>
</table>

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**Figure 3. Schematic representation of some of the signaling pathways and transcription factors that may mediate the effects of angiotensin II on gene expression. RE indicates regulatory elements of the DNA target sequences; CTM, core transcription machinery. Other abbreviations are defined in the text.**
response element of the c-fos gene promoter. Ang II–dependent phosphorylation of specific serine/threonine residues in the Elk protein results in activation of the ternary complex, increased c-fos gene transcription, and ultimately, stimulation of downstream events linked to the growth response. Ang II has also been shown to activate the stress-activated protein kinase, which is known to phosphorylate the amino terminal activation domain of the Jun protein and thereby promote the transcriptional regulatory activity of the activator protein-I complex. To the extent that Ang II promotes increased levels of intracellular calcium, it might also stimulate the activity of calcineurin phosphatase and activate the cytoplasmic nuclear factor of activated T cells (NF-ATc), a transcription factor that can influence the expression of genes involved in cardiac growth and development. Finally, several groups have noted that Ang II may modulate gene transcription through the JAK-STAT signaling pathway. This pathway mediates cytokine-induced transcriptional activation of a number of genes, including the early growth response genes such as c-fos. By inference, this suggests that Ang II can use more than one signaling pathway to promote expression of even a single gene in a target cell. This may imply simple redundancy in the signaling cascades or, alternatively, selective dominance of individual signaling pathways in different cell types or different environmental settings.

It is important to acknowledge that the reputedly superior cardiovascular and renal protective properties of converting enzyme inhibitors may prove to be more closely related to their hemodynamic effects than to their ability to attenuate Ang II–induced changes in gene expression. Nevertheless, the well-documented influence of Ang II on the expression of a wide variety of genes relevant to cardiovascular function, as well as the presumed effectiveness of ACE inhibitors in preventing many of the chronic effects of essential hypertension, suggests that further investigation into the clinical significance of the transcriptional effects of ACE inhibitors and angiotensin receptor blockers is warranted. Moreover, continued research into the mechanisms whereby Ang II influences gene expression may provide insight into the development of new transcription-modulating drugs for the prevention and treatment of essential hypertension and cardiovascular disease.

Essential Hypertension as a Complex Disorder of Gene Regulation: Treatment From the Molecular Mosaic Perspective

As we accumulate more information about the fundamental mechanisms underlying gene transcription, the opportunities for pharmacological modulation of gene expression will extend well beyond the development of converting enzyme inhibitors or ligands for intracellular receptors such as PPARα. For example, research advances on the function and regulation of key transcription factors such as nuclear factor-κB, NF-ATc, STATs, and the accessory proteins that interact with nuclear hormone receptors are likely to culminate in novel transcription-modulating drugs that will be relevant to the prevention and treatment of hypertension and various forms of cardiovascular disease.

Figure 4. Presentation of the hypertension mosaic showing the central placement of genes within the core of the mosaic. This molecular mosaic is directly modified from the hypertension mosaic of J.H. Page and illustrates the key role of genetic factors in regulating the multiple pathways involved in the pathogenesis of essential hypertension. In contrast to conventional antihypertensive agents that treat surface facets of the Page mosaic, transcription-modulating drugs can be used to modify gene expression and attack essential hypertension at the core of the mosaic. Nonpharmacological therapies that manipulate environmental factors affecting gene transcription might provide another approach to attacking core molecular determinants of essential hypertension.

Over 30 years ago, Page put forth his mosaic theory in which multiple regulatory systems were proposed to interact in the pathogenesis of hypertension. It would seem reasonable to extend the mosaic theory to the molecular level, where multiple genetic factors interact to promote essential hypertension (Figure 4). In the latter model, quantitative traits such as blood pressure and complex metabolic syndromes such as essential hypertension can be affected by alterations in gene expression, as well as by changes in gene-protein structure. Thus, Page’s concept of hypertension as a disease of “regulation” might now be viewed as encompassing the regulation of gene expression. As we enter the 21st century, it may be time to move beyond the surface facets of the blood pressure mosaic and consider the use of transcription-modulating drugs to attack essential hypertension at a more proximate step in the pathogenetic cascade, ie, at the core of the blood pressure mosaic (Figure 4). Such approaches are more closely targeted at the underlying disorder and may ultimately prove more effective in controlling the manifold clinical manifestations of essential hypertension.

References


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