Published in final edited form as:

J Cardiovasc Pharmacol. 2010 September ; 56(3): 213–214. doi:10.1097/FJC.0b013e3181f0d63f.

Novel Drugs Targeting Hypertension Revisited

George W. Booz, Ph.D.

Department of Pharmacology and Toxicology, and the Center for Excellence in Cardiovascular-Renal Research, The University of Mississippi Medical Center, Jackson, MS, USA

Three years ago *The Journal of Cardiovascular Pharmacology* published a review series on novel drugs targeting hypertension. In the current issue and the next one, a series of articles appear that discuss four new areas for drug development that have evolved in recent years and have relevance for treating hypertension and other cardiovascular diseases. Unfortunately, the need for such drugs is as great as ever. According to the most recent report of the American Heart Association, 1 in 3 adults in the United States has high blood pressure, as evidenced by having systolic blood pressure ≥ 140 mm Hg or diastolic blood pressure ≥ 90 mm Hg, being on antihypertensive medicine, or being told by their doctor or health care professional in 2 separate visits they have high blood pressure.¹ For 2010, the estimated direct and indirect cost for high blood pressure is estimated to be \$76.6 billion. The most recent statistics available from 2006 show that the overall death rate due to high blood pressure was 17.8: among white males, 15.6; black males, 51.1; white females, 14.3; and black females, 37.7. Blood pressure $>140/90$ mm Hg is found in approximately 69% of those who have a first heart attack, 77% who have a first stroke, and 74% who have congestive heart failure. Overall, almost 75% of adults with cardiovascular disease comorbidities have hypertension, which is associated with a shorter overall life expectancy. Alarming, rates of prehypertension and hypertension are increasing among children and adolescents 8 to 17 years old due in part to the obesity epidemic we currently face.

Poor control of systolic hypertension remains a principal problem in treating hypertension and further compromises risk of cardiovascular disease due to end organ damage. The latest statistics from 2003–2006 reveal that of those with high blood pressure 55.9% do not have it under control.¹ Therefore, new drug discoveries are needed to treat the majority of individuals who have high blood pressure. An additional need for novel anti-hypertensive drugs comes from the growing rates of diabetes and obesity, as well as an aging population, all factors which are associated with high blood pressure.²

An article by Dr. Hai Wang and colleagues on iptakalim leads off the series.³ Iptakalim is a novel ATP-sensitive potassium (K_{ATP}) channel opener that shows high selectivity for the cell surface SUR2B/Kir6.1 channels, which are expressed by vascular smooth muscle and endothelial cells. Because of this high selectivity, iptakalim does not exhibit the adverse side effects associated with older nonspecific K^+ channel openers that limit their use to treating severe or refractory hypertension. Iptakalim produces arteriolar and small artery vasodilation with no significant effect on capacitance vessels or large arteries, by causing cellular hyperpolarization via the opening of K^+ channels, which in turn decreases the opening probability of L-type Ca^{2+} channels. Of particular note, iptakalim is very effective in lowering the blood pressure of hypertensive humans, but not of those with normal blood pressure. In preclinical trials, iptakalim has been shown to protect against hypertension end organ damage

and to improve endothelial dysfunction. Early clinical trials in China have shown that iptakalim has a favorable safety and tolerability profile.

The next article in the series deals with heme-dependent and -independent soluble and guanylate cyclase activators and is by Drs. Priviero and Webb.⁴ Nitric oxide (NO) produced by endothelial cells activates the soluble guanylyl cyclase (sGC) of vascular smooth muscle cells, thereby increasing intracellular cGMP levels, which in turn leads to contractile relaxation and vasodilation. However, because of tolerance and pharmacokinetic considerations, the use of NO donors for managing high blood pressure has been limited in the past to treating pulmonary hypertension. Drugs that directly target sGC overcome these limitations of NO donors and hold great promise as anti-hypertensives. As discussed by Drs. Priviero and Webb, these drugs can be classified as heme-dependent sGC stimulators and heme-independent sGC activators. Because of the increased oxidative stress associated with cardiovascular diseases, the effectiveness of heme-dependent sGC stimulators may be diminished. In contrast, heme-independent sGC activators exhibit a higher affinity for the oxidized enzyme and would seem to have utility for treating systemic and pulmonary hypertension, particularly advance cases and in the elderly.

The third article in the series by Dr. Imig deals with the therapeutic utility of drugs that mimic epoxyeicosatrienoic acids (EETs) or block their breakdown by inhibiting soluble epoxide hydrolase.⁵ In the systemic circulation the EETs of endothelial cells are vasodilators and contribute to blood pressure regulation.⁶ The EETs also have protective actions against hypertension-related end organ remodeling and damage.^{6,7} One note of caution, however, should be sounded. In the pulmonary circulation EETs, generated by vascular smooth muscle cells, potentiate hypoxia-induced vasoconstriction and are implicated in vascular remodeling associated with chronic hypoxia and pulmonary hypertension.⁸

The final article comes from Dr. Roman and colleagues, who discuss the Janus-like contribution made by 20-hydroxyeicosatetraenoic acid (20-HETE) to hypertension and the challenges faced in designing drugs to target this arachidonic acid metabolite.⁹ In the vasculature, 20-HETE is a potent vasoconstrictor and promotes hypertension, while in the kidney 20-HETE inhibits Na⁺ transport and protects against hypertension-related kidney damage. Thus, a 20-HETE antagonist might be of benefit in treating patients with hypertension who have elevated vascular production of 20-HETE, while a 20-HETE mimetic could be of benefit in treating salt-sensitive hypertension. Not addressed by the authors is the possible utility in treating hypertension of combining a 20-HETE antagonist or mimetic with another class of drug. For instance, a recent study found that selective inhibition of 20-HETE formation together with a soluble epoxide hydrolase inhibitor, so as to elevate EETs, attenuated hypertension and associated end organ damage in a mouse model of angiotensin II-dependent hypertension.¹⁰ Also left unmentioned by the authors is the recent finding that mechanical forces may potentiate agonist-driven activation of vascular transient receptor potential canonical 6 (TRPC6) channels via formation of 20-HETE.¹¹ This is notable in light of a recent report that the vascular endothelium of preglomerular arterioles from patients with malignant hypertension exhibits a more prominent expression of TRPC3.¹² The TRPC channels constitute a subfamily of the TRP cation channel superfamily of proteins and were identified in the mid-1990s as candidate mammalian mechanosensitive cation channels.¹³ The 7 TRPC proteins can be further divided into 2 groups. TRPC3 and TRPC6 show an approximate 73% sequence identity and fall into the group that is directly activated by diacylglycerol. Thus, both are likely targets of activation by 20-HETE.

Hypertension is a multifactorial disorder and combination therapy is known to be essential for effective management of high blood pressure.¹⁴ Yet effective blood pressure control is not achieved in most individuals for a number of reasons: poor compliance due to the adverse side

effects of some anti-hypertensive medications, diminished drug effectiveness with time or age, life style issues, as well as drug efficacy. Thus, the need is great for novel drugs that target other contributing causes of hypertension and the processes leading to end organ damage. The four articles in this series present four different areas that hold great potential for hypertension drug development. Although, research in these areas have already produced exciting discoveries, only time will tell whether drugs arising from the knowledge that is gained will help stem the accelerating burden of hypertension in our society.

Acknowledgments

This work was supported by grants R01HL088101-04 and R01HL088101-02S1 and from the National Heart, Lung, and Blood Institute.

References

1. Lloyd-Jones D, Adams RJ, Brown TM, Carnethon M, Dai S, De Simone G, Ferguson TB, Ford E, Furie K, Gillespie C, Go A, Greenlund K, Haase N, Hailpern S, Ho PM, Howard V, Kissela B, Kittner S, Lackland D, Lisabeth L, Marelli A, McDermott MM, Meigs J, Mozaffarian D, Mussolino M, Nichol G, Roger VL, Rosamond W, Sacco R, Sorlie P, Stafford R, Thom T, Wasserthiel-Smoller S, Wong ND, Wylie-Rosett J. WRITING GROUP MEMBERS; American Heart Association Statistics Committee and Stroke Statistics Subcommittee. Heart disease and stroke statistics--2010 update: a report from the American Heart Association. *Circulation* 2010 Feb 23;121(7):e46–e215. [PubMed: 20019324]
2. Feig PU, Roy S, Cody RJ. Antihypertensive drug development: current challenges and future opportunities. *J Am Soc Hypertens*. 2010 May 26; [Epub ahead of print].
3. Pan Z, Huang J, Cui W, Long C, Zhang Y, Wang H. Targeting Hypertension With a New ATP-Sensitive Potassium Channel Opener Iptakalim. *J Cardiovasc Pharmacol*. 2010 Apr 17; [Epub ahead of print].
4. Priviero FB, Webb RC. Heme- Dependent and Independent Soluble Guanylate Cyclase Activators and Vasodilation. *J Cardiovasc Pharmacol*. 2010 Jun 21; Epub ahead of print.
5. Imig JD. Targeting Epoxides for Organ Damage in Hypertension. *J Cardiovasc Pharmacol*. 2010 Jun 7; [Epub ahead of print].
6. Lee CR, Imig JD, Edin ML, Foley J, Degraff LM, Bradbury JA, Graves JP, Lih FB, Clark J, Myers P, Perrow AL, Lepp AN, Kannon MA, Ronnekleiv OK, Alkayed NJ, Falck JR, Tomer KB, Zeldin DC. Endothelial expression of human cytochrome P450 epoxigenases lowers blood pressure and attenuates hypertension-induced renal injury in mice. *FASEB J*. 2010 May 21; [Epub ahead of print].
7. Harris TR, Li N, Chiamvimonvat N, Hammock BD. The potential of soluble epoxide hydrolase inhibition in the treatment of cardiac hypertrophy. *Congest Heart Fail* 2008 Jul-Aug;14(4):219–224. [PubMed: 18780476]
8. Loot AE, Fleming I. Cytochrome P450-Derived Epoxyeicosatrienoic Acids and Pulmonary Hypertension: Central Role of Transient Receptor Potential (TRP) C6 Channels. *J Cardiovasc Pharmacol*. 2010 Jun 24; [Epub ahead of print].
9. Williams JM, Murphy S, Burke M, Roman RJ. 20-HETE: a new target for the treatment of hypertension. *J Cardiovasc Pharmacol*.
10. Certíková Chábová V, Walkowska A, Kompanowska-Jezierska E, Sadowski J, Kujal P, Vernerová Z, Vanourková Z, Kopkan L, Kramer HJ, Falck JR, Imig JD, Hammock BD, Vanecková I, Cervenka L. Combined inhibition of 20-hydroxyeicosatetraenoic acid formation and of epoxyeicosatrienoic acids degradation attenuates hypertension and hypertension-induced end-organ damage in Ren-2 transgenic rats. *Clin Sci (Lond)* 2010 Feb 23;118(10):617–632. [PubMed: 20050826]
11. Inoue R, Jensen LJ, Jian Z, Shi J, Hai L, Lurie AI, Henriksen FH, Salomonsson M, Morita H, Kawarabayashi Y, Mori M, Mori Y, Ito Y. Synergistic activation of vascular TRPC6 channel by receptor and mechanical stimulation via phospholipase C/diacylglycerol and phospholipase A₂/ω-hydroxylase/20-HETE pathways. *Circ Res* 2009 Jun 19;104(12):1399–1409. [PubMed: 19443836]
12. Thilo F, Loddenkemper C, Berg E, Zidek W, Tepel M. Increased TRPC3 expression in vascular endothelium of patients with malignant hypertension. *Mod Pathol* 2009 Mar;22(3):426–430. [PubMed: 19136933]

13. Watanabe H, Murakami M, Ohba T, Takahashi Y, Ito H. TRP channel and cardiovascular disease. *Pharmacol Ther* 2008 Jun;118(3):337–351. [PubMed: 18508125]
14. Epstein BJ. Improving blood pressure control rates by optimizing combination antihypertensive therapy. *Expert Opin Pharmacother*. 2010 Jun 30; [Epub ahead of print].