Is There a New Treatment for Hypertensive Disease in the Horizon?
Role of Soluble Guanylate Cyclase

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Left ventricular hypertrophy (LVH) and fibrosis have received special attention as possible therapeutic targets in preventing cardiovascular complications of hypertension. Suppression of neurohormonal factors that predispose to target organ damage, in addition to blood pressure (BP) reduction, seems to be of importance in modulating cardiac remodeling and fibrosis in hypertensive heart disease. In the normal heart, the effects of endogenous hypertrophic/proliferative factors, including angiotensin II (Ang II), aldosterone, and inflammatory cytokines, such as transforming growth factor-β, growth factors, and catecholamines, are balanced by the action of growth-inhibiting/antiﬁbrotic factors, including NO, natriuretic peptides, and bradykinin.

Previous studies have shown that atrial natriuretic peptide (ANP) modulates cardiac hypertrophy and ﬁbrosis in response to a variety of hemodynamic stresses.1–3 In the setting of hypertension or in the absence of the counterregulatory effects of ANP signaling, as in the ANP null (Nppα−/−) or heterozygous (Nppα+/−) mouse or the mouse lacking natriuretic peptide type A receptors (Npr−/−), the unopposed profibrotic/hypertrophic factors predominate, and LVH with interstitial and perivascular ﬁbrosis develops. In vitro studies have demonstrated that ANP inhibits cardiac ﬁbroblast proliferation, myoﬁbroblast transformation, and expression of extracellular matrix, including collagen, via a signaling pathway that involves particulate guanylate cyclase, cGMP, and protein kinase G.4 This cardioprotective signaling cascade has attracted the interest of clinicians because of the recent demonstration that the phosphodiesterase 5 inhibitor silde-nafil (Viagra) reverses cardiac hypertrophy and remodeling in mice subjected to pressure overload stress.5 Unfortunately, no orally active analog of ANP or other stimuli of particulate guanylate cyclase activity is available for clinical use.

The report by Masuyama et al6 is of major interest in that it demonstrates that BAY41-2272, a novel orally active NO-independent stimulator of soluble guanylate cyclase (sGC) that lacks of phosphodiesterase 5 inhibitory activity inhibits cardiac hypertrophy and fibrosis in rats with Ang II–induced hypertension. This important study provides the first demonstration that activation of sGC can prevent hypertensive cardiac pathology in a manner similar to activation of particulate guanylate cyclase by ANP.

Previous observations that expression/activation of sGC is reduced in the vasculature of aging hypertensive animals in association with progressive vascular dysfunction have deﬁned sGC as a key target of the hypertensive disease process and a potential site for therapeutic intervention.7,8 Functional consequences of the resultant decrease in cGMP generation include attenuated vasodilation, increased vascular remodeling, cardiac hypertrophy/remodeling, and an increased tendency for platelet aggregation, all of which predispose to cardiovascular disease events (Figure). In addition, hypertension-associated oxidative stress impairs NO-mediated control of vascular function through sGC by increasing levels of superoxide, which reacts with NO to form the powerful oxidant ONOO−. All of these pathologic mechanisms, which involve reducing the bioavailability of endogenous NO, could be bypassed by direct activation of sGC.

Masuyama et al6 tested the therapeutic potential of stimulating endogenous sGC activity in a rat model of Ang II–induced hypertension and cardiac remodeling. They treated Wistar rats that were receiving Ang II with BAY41-2272 at a low (2 mg/kg per day) or high (10 mg/kg per day) dose for 14 days. High-dose BAY41-2272 attenuated the Ang II–induced rise in BP and completely prevented LVH; the low dose inhibited perivascular and interstitial myocardial ﬁbrosis and reduced the number of activated ﬁbroblasts surrounding the coronary arteries without lowering BP or preventing LVH. Low-dose BAY41-2272 also downregulated LV collagen I and transforming growth factor-β mRNA levels. These effects of BAY41-2272 were accompanied by increased cGMP levels in the LV and in cultured cardiac ﬁbroblasts, resulting in reduced thymidine incorporation into the cells. Thus, BAY41-2272 prevented Ang II–induced cardiac remodeling and ﬁbrosis via a local, cGMP-dependent mechanism that is independent of BP.

The article by Mayusuma et al6 adds to the literature documenting beneﬁcial effects of BAY41-2272 in animal models of systemic hypertension,7,8 heart failure,9 and pulmonary hypertension.10 Importantly, BAY41-2272 produced favorable hemodynamic effects comparable to those seen with nitroglycerin infusion in a canine model of heart failure.9 In particular, despite a lower BP, BAY41-2272 preserved glomerular ﬁltration rate and effected a mild diuresis without activating the renin–angiotensin–aldosterone system. This renoprotective effect is likely to be of major benefit in patients with systolic dysfunction and renal impairment.
In conclusion, targeting sGC for the treatment of cardiovascular disorders in humans is of great interest, because the NO/sGC pathway seems to play an important role in maintaining physiological heart and vascular function and preventing hypertrophic/fibrotic injury and endothelial dysfunction. BAY41-2272, an orally active stimulator of sGC, may represent a new class of drugs, complementary to currently established therapies for chronic cardiovascular disorders. Clinical trials are warranted to address the safety and efficacy of this novel therapy in humans.

**Disclosures**

None.

**References**

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