Loss of Vascular Regulation by Soluble Guanylate Cyclase Is Emerging as a Key Target of the Hypertensive Disease Process

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The soluble form of guanylate cyclase (sGC) is well established as a primary target for the actions of NO. It is a key regulator of vascular smooth muscle force and growth through its production of cGMP. In this issue of Hypertension, Klöss et al provide evidence that aged hypertensive rats have decreased levels of an mRNA-binding protein human R (HuR), which stabilizes the mRNA for the subunits of sGC and enables expression of this important enzyme. Previous work from this group showed how the HuR protein functions to stabilize the mRNA for sGC and that the expression of HuR is controlled by the availability of cGMP, whereas cGMP appears to inhibit the expression of this mRNA-stabilizing protein. Because hypertension is thought to generally decrease sGC expression and the stimuli for sGC activation, the decrease in HuR expression is likely to be through a mechanism that is independent of the previously identified interactions of cGMP with this system. A model describing the potential influence of hypertension on relationships between these systems in controlling the expression and activity of sGC is shown in the Figure. The decrease in HuR has many implications for controlling processes potentially involved in the progression of hypertension that are discussed in the article by Klöss et al. However, the influence of HuR on the expression of sGC may be a primary factor in the progression of hypertension. cGMP generated by sGC appears to coordinate multiple signaling mechanisms that control vascular force and processes involved in remodeling of the vessel wall that are potentially important during the progression of hypertension.

Previous work has identified important roles for oxidative stress–associated processes in development and progression of multiple forms of hypertensive disease in humans and animal models. One of the key targets of hypertension-associated oxidative stress is the impairment of NO-mediated control of vascular function through sGC by the increased levels of superoxide seen in hypertensive diseases. For example, increased intraluminal pressure appears to be a direct stimulus for oxidant activation in endothelium and vascular smooth muscle of the artery wall. Whereas superoxide scavenges NO, resulting in the formation of peroxynitrite, this oxidant and other reactive oxygen species may further decrease NO biosynthesis by oxidizing the tetrahydropyropterin cofactor of NO synthase, and this is associated with increased superoxide generation by this enzyme. Peroxynitrite and other oxidants may also impair sGC regulation by oxidizing thiol and heme sites on sGC. Although increased peroxide is a stimulus for promoting NO synthase expression and activity in endothelium, the importance of this feedback-type mechanism in hypertensive diseases processes is not known. Overall, hypertension appears to be associated with oxidative stress in the vascular wall and impaired regulation of sGC, which potentially results from a combination of decreased expression of sGC, a loss of stimulation of cGMP production by NO, and perhaps a direct inactivation of sGC by reactive oxygen species and NO-derived oxidant species.

Aged hypertensive rats have been reported to show a decreased expression of sGC through mechanisms that remain to be explained. Previous studies on the regulation of sGC expression suggest the existence of several pathways through which hypertensive-related oxidant processes could influence the expression of sGC. The promoter region of sGC in mice has several sites for redox-regulated promoters that
could be influenced by conditions that potentially exist in hypertension. However, the importance of sGC regulation by these pathways is not understood. Whereas interactions of oxidant conditions with processes that control sGC in hypertensive diseases suggest that cGMP signaling would be impaired, decreased regulation by cGMP should promote increased HuR and sGC expression. However, the observation reported in this issue of *Hypertension* of a decreased expression of HuR in aged hypertensive rats indicates that hypertension potentially causes a novel defect in the regulation of this system. Although oxidant conditions that exist in the vessel wall could be hypothesized as a contributing factor to decreased HuR expression, this potential mechanism remains to be investigated.

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**References**


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