Regulator of G-Protein Signaling-2 as a Candidate Gene
The Road to Hypertension or Just Another Roadside Marker?
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The “mosaic theory” of hypertension has been the prevailing dogma since its enunciation more than a half century ago. However, the ongoing search has been to determine which of the myriad of alterations in blood pressure regulatory systems occurs earliest in the process and are critical in the maintenance of the hypertensive state. Much of that focus has been directed to the determinants of increased peripheral resistance—perhaps the hallmark of the hypertensive state. The mechanisms underlying this abnormality reflect a combination of both structural and functional factors.

From a functional perspective, peripheral resistance reflects a net balance between vasoconstrictor and vasodilator mechanisms. Defects in vasodilator mechanisms and enhancement of vasoconstrictor mechanisms have been described in human hypertension as well as in animal models. Central among these mechanisms have been alterations in G-protein-coupled receptor (GPCR) signaling pathways. Alterations in GPCR-signaling pathways in the hypertensive state are probably best explained by alterations downstream from the receptor. For those GPCRs linked to G, and adenylyl cyclase activation, the impairment in GPCR/G-protein “coupling” reflects both decreased G-protein function as well as the impact of increased expression/activity of the G-protein receptor kinases that interdict GPCR/G-protein signaling.1 For those mechanisms linked to vasoconstrictor process (via either Gi or Gq) the alterations also appear to be generalized across a range of receptors, consistent with a “downstream” effect.2 For Gq-linked systems, enhanced Gi function has been described in hypertension.3 However, for Gi-linked systems the locus of the defect is less clear.

Alterations in GPCR signaling have often been assumed/inferred to be secondary events. For example, it was a common “belief” that the defect in β adrenergic–mediated vasodilation was secondary to the effect of longer-term desensitization via elevations in sympathoadrenal activity. However, in several settings these defects have now been shown to be still evident in vitro and following prolonged culture (eg, the finding that impaired β adrenergic–mediated signaling in spontaneously hypertensive rats is still evident in cultured vascular smooth muscle cells3). These findings have emphasized a potential role of a primary and possibly “genetic” basis for these downstream alterations in GPCR signaling. Parenthetically, the cellular biology of GPCR signaling alterations in hypertension as outlined above would not suggest an important role of discrete variants of individual GPCRs (ie, as for the individual adrenoceptor variants that have been widely studied, but inconclusively4).

Dysfunctional genetic variants of the G-protein β3 subunits1 (GNB3, that is principally linked to Gi activation), the α subunit of G, (GNAS1),2 and the G protein receptor kinase GRK45 (GRK4 that predominantly impacts on G-mediated function) have been proposed as potential genetic regulators of GPCR-mediated vascular function with implications in hypertension (Figure). The current article by Riddle et al,6 published in this issue of Hypertension, proposes an additional candidate gene—regulator of G-protein signaling-2 (RGS2).

RGS2 is a member of the family of G-protein–associated proteins that act to facilitate GTPase activity and, hence, “turn off” G-proteins.7 Among G-proteins, their effect is particular to the actions of G, family proteins (although some effects of RGS2 to attenuate Gi signaling have also been reported). Further, an RGS2 knockout mouse model does demonstrate increased blood pressure.8 Thus, alterations in RGS2 function would seem to be critical for regulation of the net effect of activation of both vasodilator and vasoconstrictor signaling pathways and hence be an obvious candidate gene in the development of hypertension.

Recent studies by Yang et al identified that among a range of genetic variations of RGS2 characterized in normotensive and hypertensive Japanese subjects, an insertion/deletion (I/D) variant at 1891 to 1892 (in the noncoding region of the gene) was more commonly expressed in hypertensive subjects (although some effects of RGS2 to attenuate Gi signaling have also been reported). Further, an RGS2 knockout mouse model does demonstrate increased blood pressure.8 Thus, alterations in RGS2 function would seem to be critical for regulation of the net effect of activation of both vasodilator and vasoconstrictor signaling pathways and hence be an obvious candidate gene in the development of hypertension.

The search for candidate genes important in the etiology of hypertension has been tortuous and often unproductive. Notwithstanding, further examination of a potential causal link between expression of variant RGS2 genes and hypertension may be warranted. However, the articles by Yang et al and Riddle et al must be seen for what they are—important, but only the initial stop en route to proving that RGS2 genetic alterations have any causal significance in hypertension. First, the biological impact of expressing this RGS2 variant is

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unknown (i.e., whether associated with increased function, decreased function, or no impact). This will require assessment at cellular levels to determine whether this variant, seen in a noncoding region, results in differential protein expression of RGS2 either quantitatively or qualitatively (perhaps in the expression of an alternate splice variant). Further, it will need to be determined whether expression of this variant results in alterations in vascular reactivity profiles in vivo. Beyond that it would need to be determined whether expression of a dysfunctional variant of RGS2 (if that occurs) really matters. RGS2 expression is highly regulatable. For those of us who have done microarray studies in the field, RGS2 often appears among the list of genes that demonstrate the greatest extent of regulation across a broad range of stimuli/conditions. Thus the relative impact of any constitutive differences in RGS2 activity on a genetic basis (versus the broad range of physiological/pathological regulation of RGS2 activity that occurs) needs to be established to understand the potential impact of these findings. Last, the ethnic specificity of these findings would suggest that the impact of this variant will only be evident in discrete haplotypes. Thus, given the likelihood that expression of any individual variant may be important only when part of an unfavorable haplotype set (perhaps including unfavorable G-protein and GRK genetic variants), the current findings may only be evident in discrete haplotypes. Therefore, given the likelihood that expression of any individual variant may be important only when part of an unfavorable haplotype set (perhaps including unfavorable G-protein and GRK genetic variants), the current findings may only be evident in discrete haplotypes. Thus, given the likelihood that expression of any individual variant may be important only when part of an unfavorable haplotype set (perhaps including unfavorable G-protein and GRK genetic variants), the current findings may only be evident in discrete haplotypes.

In total, we are a long way from determining whether expression of this genotype is of a causal importance or is yet another marker on the road to hypertension (but ultimately not directly linked to the pathogenesis of the disease). However, we would also suggest that based on the current findings and the biological plausibility of a role for this candidate gene, this trip may be well worth the ride.

References