A Role for G-protein-coupled Receptor Kinases in Hypertension

By Robert Gros

Hypertension is the most common cardiovascular disease and remains an important risk factor for myocardial infarction, stroke, and renal failure. It has been estimated that 95% of all Canadians will develop hypertension if they live an average lifespan. Therefore a better understanding of the mechanism(s) involved in the development and/or maintenance of hypertension will be critical to gain better insight into the disease and perhaps enable the development of novel treatment strategies.

In hypertension, the basic hemodynamic abnormality is increased peripheral resistance, which reflects a combination of structural and functional factors. On a functional level, peripheral resistance is a delicate balance between factors that cause vasodilation and those that mediate vasoconstriction. In vascular smooth muscle cells (VSMCs), an important mechanism which mediates vasodilation are G-protein-coupled receptors (GPCRs) linked to adenyl cyclase activation through the Gs-proteins (also known as the stimulatory G-protein). The beta-adrenergic receptor represents the prototypical vasodilatory receptor in VSMCs (although some of the beta-adrenergic-mediated vasodilation is endothelial-dependent). However, a number of other important GPCRs linked to adenyl cyclase activation are also expressed in VSMCs including: adenosine, glucagon, bradykinin receptors and others. In endothelial cells, GPCRs linked to vasodilatory responses appear more complex and involve GPCRs linked to Gs (adrenergic receptors), Gi (muscarinic receptors) and Gq (endothelin-B receptors) resulting in release of vasodilatory mediators such as nitric oxide, endothelium-derived hyperpolarizing factor(s) or prostacyclin. On the vasoconstrictor side, GPCRs such as endothelin, alpha-adrenergic and angiotensin receptors (and others) are linked to the activation of phospholipase C and/or inhibition of adenyl cyclase via the activation of Gq-proteins and/or Gi-proteins in VSMCs.

Defects in GPCR-mediated Vasodilation in Hypertension

The most consistently described vascular GPCR-related defects in human and animal models of hypertension is impairment in responses to activation of GPCRs linked to Gs-proteins, resulting in impaired vasodilation during the hypertensive state. The impairment in GPCR-mediated vasodilation appears to be at the level of the receptor, since either direct-acting vasodilators (e.g., nitroglycerin or nitroprusside) or vasodilators acting distal to the receptor (e.g., forskolin or dibutyryl cyclic AMP) were not comparably impaired. This implies that impairment in GPCR-mediated vasodilation is a functional uncoupling of these GPCRs from the Gs-proteins. The efficiency with which GPCRs interact with their G-proteins is in part dependent on the phosphorylation state of the receptor. GPCR phosphorylation is mediated by several different kinases, including the second-messenger dependent protein kinases such as protein kinase A and protein kinase C and by members of the G-protein receptor kinase family (GRKs).

GPCR Aactivation and Desensitization

Activation of GPCRs following agonist binding induces a conformational change that promotes the exchange of GDP for GTP on the Gα subunit and allows the dissociation of the Gα and Gβγ subunits (Figure 1). Subsequently these G-protein subunits will interact and regulate the activity of a number of other effector molecules, such as adenyl cyclase, phospholipase C, ion channels, tyrosine kinases and many others. This conformational change also allows the GPCRs to bind one (or more) of the GRKs (Figure 1). The binding of GRKs to the agonist-occupied receptor promotes the phos-
Hypertension demonstrated that GRK2 protein expression increased blood pressure. In addition, we stimulated adenylyl cyclase activity and increases in GRK2 expression and activity was correlated with reduced beta-adrenergic-mediated vasoconstriction. This increase in GRK2 expression and activity was increased in human hypertensive models. We have previously demonstrated a potential critical role for GRKs in the pathogenesis and/or maintenance of hypertension.

Where Do We Go From Here?

Although GRK2 and GRK5 have been implicated in the pathogenesis and/or maintenance of hypertension, important questions remain to be addressed. Why does increased GRK protein expression preferentially affect those GPCRs linked to vasodilation, as evident during the hypertensive state, since GRKs are capable of mediating the phosphorylation of many different GPCRs, including those linked to vasodilation and vasoconstriction? In addition, the contribution of selective GRK isoforms to the development and/or maintenance of the hypertensive phenotype is unclear. Therefore, ongoing studies in my laboratory are examining the role(s) of GRKs in regulating GPCR-mediated vascular function under physiologic and hypertensive conditions.

Conclusion

A better understanding of the regulation of vascular GPCRs by GRKs will enable the appropriate assessment of novel strategies for the treatment and/or prevention of hypertension and potentially other cardiovascular diseases linked to abnormal GPCR function and GRK regulation.

Additional Reading:


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