

Increased pressure on G protein-coupled receptor kinases.

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Editorial

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In a report published in this issue of the *Journal*, Gros et al. (1) provide convincing evidence that increased expression of a specific G protein-coupled receptor kinase may underlie the blunted β -adrenergic responsiveness generally observed in hypertensive patients. G protein-coupled receptor kinases represent a family of at least six protein kinases (GRK1–6), discovered for their ability to regulate the function of G protein-coupled receptors. Rhodopsin kinase (GRK1) and the β -adrenergic receptor kinase (β ARK1; GRK2), which selectively phosphorylate and regulate the function of the visual pigment rhodopsin and of the β -adrenergic receptors (β AR) for catecholamines, respectively, can be considered prototypical of this kinase family. Their role in controlling signaling efficacy upon sustained stimulation has been well-established. In particular, phosphorylation of the β_2 AR by β ARK has been shown to play a key role in the development of rapid agonist-induced desensitization (for review see references 2 and 3). Indeed, β ARK-mediated phosphorylation of serine and threonine residues in the distal portion of the carboxyl terminus of the receptor (4) has been shown to promote the association of the protein β -arrestin with the β_2 AR thus inhibiting functional coupling of the receptor to its cognate G protein and preventing signal transduction (5). This permits the cell to adapt to its environment and plays a major role in the sorting and integration of the information detected at the receptor level.

Obviously, alterations of such normal regulatory mechanisms could lead to certain pathological conditions related to hyper- or hyposensitivity of signal transduction systems. In fact, the depressed β -adrenergic responsiveness observed in cardiovascular diseases, such as heart failure and hypertension, has often been proposed to reflect an exaggerated agonist-promoted desensitization (for review see reference 6). One simple hypothesis is that the increased catecholamine release resulting from the elevated sympathetic activity accompanying these pathological states would promote agonist-induced desensitization of the β AR as part of a protective compensatory mechanism. In the long run, however, the chronic desensitization would contribute to the progression of the diseases by blunting the cardiac inotropic and the peripheral vasodilatory responses to β -adrenergic stimulation. In 1993, Ungerer et al. (7) brought more support to this idea and provided a molecular correlate to the functional hypothesis by showing that the β AR down-regulation and functional uncoupling observed in the heart of patients with congestive heart failure was accompanied by an increased expression of β ARK, measured both as an elevation of the kinase activity and of its mRNA levels. The authors then proposed that this increase in β ARK activity contributed to the exaggerated β -adrenergic desensitization found in heart failure patients.

In this issue, Gros et al. (1) report that increased β ARK activity may also contribute to the depressed β -adrenergic responsiveness observed in hypertensive patients. Indeed, they found that in a population of hypertensive patients, characterized by a blunted β AR reactivity as assessed by a reduced isoproterenol-stimulated adenylyl cyclase activity in isolated lymphocytes, both the quantity and the activity of β ARK-1 are increased in circulating lymphocytes. Strikingly, a good inverse correlation was observed between the quantity of immunoreactive β ARK-1 and the β -adrenergic responsiveness in these cells. Given that overexpression of β ARK-1 has been shown, in transfected cells and transgenic animals, to promote exaggerated agonist-induced desensitization (8, 9), it may be reasonable to propose that the blunted β -adrenergic-stimulated adenylyl cyclase activity results, at least in part, from the increased β ARK expression. In light of the general belief that a reduced β -adrenergic-mediated vasodilatation contributes to the maintenance and exacerbation of elevated blood pressure in a population of hypertensive patients, the results of Gros et al. may point to β ARK-1 as a potential culprit in the pathogenesis of hypertension. The change observed in β ARK-1 activity is rather selective since no alteration was found in GRK-5, GRK-6, or in cAMP-dependent protein kinase activity. This selectivity may turn out to be clinically relevant, as a unique enzyme may represent the pharmacological target to prevent the development of exaggerated β AR desensitization.

Despite the convincing evidence presented by Gros et al., it is too early to conclude that the increased β ARK expression observed indeed contributes significantly to the pathological elevation in blood pressure. For one, these changes were studied in circulating lymphocytes and must be confirmed in physiologically more relevant tissues, such as vascular smooth muscle and cardiac cells, before any firm conclusion can be drawn. Second, the causal link between the elevation in β ARK-1 activity and the reduced β -adrenergic responsiveness in patients must be established experimentally. One way to achieve this would be to experimentally manipulate the expression level of β ARK-1. In that respect, significant efforts are required to investigate the mechanisms leading to the elevation of β ARK expression in both heart failure and hypertension. One likely candidate would be the increased stimulation of the β AR itself as a consequence of the elevated sympathetic tone characteristic of these pathological states. Gros et al. argue that this may not be the case in hypertensive patients since dietary salt restriction, a maneuver associated with increased sympathetic activity, corrects the defect in β AR responsiveness. Nevertheless, this possibility should be directly assessed by studying the effects of chronic administration of β -blockers with or without inverse agonistic properties (10) on the expression level of β ARK-1. Alternatively, the possibility that elevated β ARK levels may represent genetic variability that could have an impact on the susceptibility of individuals to develop sustained high blood pressure is also appealing and worth testing.

In conclusion, the work by Gros et al. certainly provides evidence suggesting β ARK as a potential factor involved in the development and maintenance of human hypertension.

However, much work is required before a conclusive demonstration of its involvement, and of its clinical importance, is made.

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References

1. Gros, R., J.L. Benovic, C.N. Tan, and R.D. Feldman. 1997. G-protein coupled receptor kinase activity is increased in hypertension. *J. Clin. Invest.* 99: 2087–2093.
2. Benovic, J.L., M. Bouvier, M.G. Caorn, and R.J. Lefkowitz. 1988. Regulation of adenylyl cyclase-coupled β -adrenergic receptors. *Annu. Rev. Cell Biol.* 4:405–428.
3. Kobilka, B.K. 1992. Adrenergic receptors as models for G protein-coupled receptors. *Annu. Rev. Neurosci.* 15:87–114.
4. Bouvier, M., W.P. Hausdorff, A. DeBlasi, B.K. Kobilka, B.F. O'Dowd, M.G. Caron, and R.J. Lefkowitz. 1988. Removal of phosphorylation sites from the β_2 -adrenergic receptor delays onset of agonist-promoted desensitization. *Nature (Lond.)* 333:370–372.
5. Pitcher, J., M.J. Lohse, J. Codina, M.G. Caron, and R.J. Lefkowitz. 1992. Desensitization of the isolated β_2 -adrenergic receptor by β -adrenergic receptor kinase, cAMP-dependent protein kinase, and protein kinase C occurs via distinct molecular mechanisms. *Biochemistry*. 31:3193–3197.
6. Brodde, O.E., M.C. Michel, and H.R. Zerkowski. 1995. Signal transduction mechanisms controlling cardiac contractility and their alterations in chronic heart failure. *Cardiovasc. Res.* 30:570–584.
7. Ungerer, M., M. Böhm, J.S. Elce, E. Erdmann, and M.J. Lohse. 1993. Altered expression of β -adrenergic receptor kinase and β_1 -adrenergic receptors in the failing human heart. *Circulation*. 87:454–463.
8. Pippig, S., S. Andexingert, K. Daniel, M. Puzicha, M.G. Caron, and R.J. Lefkowitz. 1993. Overexpression of β -arrestin and β -adrenergic receptor kinase augment desensitization of β_2 -adrenergic receptors. *J. Biol. Chem.* 268:3201–3208.
9. Koch, W.J., H.A. Rockman, P. Sannama, R. Hamilton, R.A. Bond, C.A. Milano, and R.J. Lefkowitz. 1995. Cardiac function in mice overexpressing the β -adrenergic receptor kinase or a β ARK inhibitor. *Science (Wash. DC)*. 268: 1350–1353.
10. Chidiac, P., T. Hebert, M. Dennis, and M. Bouvier. 1994. Inverse agonist activity of β_2 -adrenergic antagonists. *Mol. Pharmacol.* 45:490–499.