Editorial

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 (βARK1; GRK2), which selectively phosphorylate and regulate the function of the visual pigment rhodopsin and of the β-adrenergic receptors (βAR) 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_2AR by βARK has been shown to play a key role in the development of rapid agonist-induced desensitization (for review see references 2 and 3). Indeed, βARK-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_2AR 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 βAR 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 βAR downregulation and functional uncoupling observed in the heart of patients with congestive heart failure was accompanied by an increased expression of βARK, measured both as an elevation of the kinase activity and of its mRNA levels. The authors then proposed that this increase in βARK activity contributed to the exaggerated β-adrenergic desensitization found in heart failure patients.

In this issue, Gros et al. (1) report that increased βARK 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 βAR reactivity as assessed by a reduced isoproterenol-stimulated adenylyl cyclase activity in isolated lymphocytes, both the quantity and the activity of βARK-1 are increased in circulating lymphocytes. Strikingly, a good inverse correlation was observed between the quantity of immunoreactive βARK-1 and the β-adrenergic responsiveness in these cells. Given that overexpression of βARK-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 βARK 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 βARK-1 as a potential culprit in the pathogenesis of hypertension. The change observed in βARK-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 βAR desensitization.

Despite the convincing evidence presented by Gros et al., it is too early to conclude that the increased βARK 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 βARK-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 βARK-1. In that respect, significant efforts are required to investigate the mechanisms leading to the elevation of βARK expression in both heart failure and hypertension. One likely candidate would be the increased stimulation of the βAR 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 βAR 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 βARK-1. Alternatively, the possibility that elevated βARK 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 βARK as a potential factor involved in the development and maintenance of human hypertension.

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

Michel Bouvier
Department of Biochemistry
and Groupe de Recherche sur le Système Nerveux Autonome
Université de Montréal

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