Editorial Comment

Adenosine and Cardioprotection in Chronic Heart Failure: Genes and Protein Expression

Ichiro HISATOME[1)]

(*Hypertens Res* 2007; 30: 757–758)

Key Words: **adenosine, cardioprotection, gene expression, heart failure**

Adenosine, a natural metabolic autacoid, ubiquitously exists inside or outside of all living cells. It plays multiple physiological roles to maintain the homeostasis of cells and thus of tissues and organs including the heart.

Adenosine is released from cells and interacts with specific cell membrane receptors to modulate cell function in an autocrine or paracrine manner (*1*–*3*). The events modulated *via* adenosine receptors include decreases in heart rate, contractility, and smooth muscle tone; the induction of sedation; the release of neurotransmitters; and the promotion of glycolysis and lipolysis as well as the modulation of renal, platelet, leukocyte, and endothelial cellular functions. In cardiovascular systems, adenosine mediates the negative chronotropic actions on the sinus node and the atrioventricular node (*1*). Its direct negative chronotropic and dromotropic properties are the basis for its wide diagnostic and therapeutic application in patients with supraventricular tachycardia (*4*, *5*). On the other hand, several lines of evidence suggest that adenosine is cardioprotective in patients with congestive heart failure (CHF) and ischemic heart disease (*6*, *7*), since adenosine is believed to be cardioprotective against CHF *via* 1) the attenuation of catecholamine release, β-adrenoreceptor–mediated myocardial hypercontraction, and myocardial Ca^{2+} overload; 2) the increases in coronary blood flow; and 3) the inhibition of platelet and leukocyte activation.

Adenosine is produced from AMP *via* dephosphorylation by 5′-nucleotidase located in the cytosol of the cardiac cells, together with the significant contribution of its formation from *S*-adenosyl homocystine (SAH) by SAH hydrolase. Adenosine is degraded by adenosine deaminase and adenosine kinase. Adenosine interacts with A_1, A_{2a}, A_{2b} and A_3 receptors. However, the modulation of adenosine receptors and the degradation of endogenous adenosine in CHF are not fully understood.

The intriguing and timely article by Asakura *et al*. in the present issue of *Hypertension Research* (*8*) provides new evidence that impairment of adenosine-related systems significantly contributes to the pathophysiology of CHF. They show that the gene expressions of adenosine A_1, A_{2a}, A_{2b}, and A_3 receptors, adenosine deaminase, and cytosolic 5′-nucleotidase were decreased in human failing myocardium, while those of adenosine receptor, adenosine kinase, and ecto 5′-nucleotidase were no different than those in nonfailing myocardium. In accordance with the impaired gene expression of adenosine deaminase, its enzyme activity was also decreased with the higher cardiac adenosine levels in CHF patients with New York Heart Assciation (NYHA) II-III than in patients with NYHA I. This finding may throw a brilliant light on the adenosine's role in the pathophysiology of CHF, because this is the first study to show direct evidence that adenosine deaminase is related to CHF.

What are the roles of the down-regulation of the gene expression of adenosine deaminase, and of the modulated activities of adenosine deaminase in CHF? Since the decrease in adenosine deaminase activity contributes to the increase in adenosine production, which is believed to be cardioprotective, these changes are thought to compensate for the down-regulation of adenosine receptors and the pathophysiology of

From the [1)]Division of Regenerative Medicine and Therapeutics, Department of Genetic Medicine and Regenerative Therapeutics, Institute of Regenerative Medicine and Biofunction, Tottori University Graduate School of Medical Science, Yonago, Japan.

Address for Reprints: Ichiro Hisatome, M.D., Ph.D., Division of Regenerative Medicine and Therapeutics, Department of Genetic Medicine and Regenerative Therapeutics, Institute of Regenerative Medicine and Biofunction, Tottori University Graduate School of Medical Science, Nishichou 86, Yonago 683–8503, Japan. E-mail: hisatome@grape.med.tottori-u.ac.jp

Received May 28, 2007.

CHF. Furthermore, the present study may be consistent with the report by Loh *et al*. (*9*) showing that CHF patients with the AMP deaminase mutation, whose plasma adenosine levels are increased because of inability to deaminase AMP, have a better prognosis than patients without that mutation.

It would be intriguing to learn whether or not the augmentation of adenosine levels in plasma could reveal the cardioprotective effects of adenosine in patients with CHF. Kitakaze and his colleagues (*7*, *10*) previously reported that the plasma level of adenosine was significantly elevated in patients with CHF and that the magnitude of the increase correlated well with the NYHA classification in these patients. Asakura *et al*. (*8*) report that dipyridamole, an adenosine potentiator, increased the plasma level of adenosine associated with decreasing the severity of CHF, suggesting the elevation of the plasma level of adenosine pharmacologically compensates for the impairment of the adenosine-related signal and exerts cardioprotective effects in patients with severe CHF.

The findings of all of these studies, when taken together, suggest that the down-regulation of adenosine receptors would impair the adenosine-related signal and thus have a deleterious effect on cardiovascular function in CHF, the pathophysiology of which accumulates adenosine by shutting down adenosine deaminase (ADA) gene expression in the heart. Therefore, a pharmacological intervention to augment the plasma level of adenosine may open a new avenue for the treatment of CHF.

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