FORUM MINIREVIEW

Development and Application of Chymase Inhibitors

Preface

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An obligation of pharmacology is the development of new drugs. At the symposium on "Development and application of chymase inhibitor" held at the 75th Annual Meeting of The Japanese Pharmacological Society (March 13, 2002; Kumamoto), we presented the chymase inhibitor as an entirely new drug and discussed its development and putatively clinical application of chymase inhibitors. This series of Forum Minireviews is based on this symposium.

Inhibitors of the renin-angiotensin (RA) system have been originally developed for antihypertensive agents and are now used widely as first choice for antihypertension treatment. However, these agents provide not only an antihypertensive effect but also have a preventive effect against tissue damage associated with hypertension. Therefore, these evidences led us to consider that a tissue protective agent should be a real antihypertensive agent. In 1984, we found that a serine protease, which did not belong to the RA system, produced angiotensin II (Ang II) from angiotensin I (Ang I). This enzyme was identified as chymase. In this Society in 2000, the pathophysiological role of Ang II produced by chymase was adopted as a symposium topic for the first time in the world, and it was demonstrated that Ang II, mediated by chymase, played an important role in developing tissue damage in various diseases models. This symposium in 2002 reflects the accumulation of knowledge achieved over the past two years.

Nakajima and Naya report the development of a chymase inhibitor that can be administered orally and the pathologic role of chymase in fibrosis after inflammation by using their chymase inhibitor.

Suzuki et al. report on the development of a recombinant

human chymase produced from *Bombix mori* and the development of a kit for measuring the blood chymase level by using antichymase antibodies produced with this recombinant chymase. This system might be useful for the clinical study of chymase.

Imada et al. show the efficacy of an inhibitor they developed toward atopic dermatitis by oral administration. In a mouse model, they evaluated the efficacy of the inhibitor by using severity of itching and IgE levels as indicators.

Sukenaga et al. report that their original chymase inhibitor is orally active and effective for the remodeling after inflammation. This inhibitor is effective for prevention of fibrosis by using a hamster myocardial-infarction model and a hamster pulmonary-fibrosis model.

Takai and Miyazaki show simultaneous increase of chymase activity and number of mast cells in canine arteries injured by a balloon catheter or canine graft veins. In these models, they clearly indicate that chymase inhibitors and Ang II receptor antagonists, but not ACE inhibitors, are effective for preventing proliferating lesions in vascular tissues.

This symposium is also the first memorial one on chymase inhibitors in the world. These articles on the representative chymase inhibitors presented here clearly show possibilities for the clinical application of these compounds. In this symposium, we place the chymase inhibitor as a leading drug in a new category of tissue-protective agents, perhaps exceeding the RA system inhibitors whose applications are limited in the hypertensive patients with cardiovascular diseases.

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