Endothelin-1 Production and Its Involvement in Cardiovascular Diseases

○Mamoru Ohkita, Masanori Takaoka and Yasuo Matsumura
(Osaka Univ. Pharmaceut. Sci.)

Endothelin (ET) has been implicated in the pathogenesis of several cardiovascular disorders because of their powerful vasoconstrictor and growth-promoting properties. The ET family consists of three isoforms, ET−1, ET−2 and ET−3. ET−1 appears to be the predominant member of the family generated by vascular endothelial cells. In view of the multiple cardiovascular actions of ET−1, there has been much interest in its contribution to the pathophysiology of hypertension and arteriosclerosis. We have been investigating the roles of ET_A and ET_B receptors in ET−1-related cardiovascular diseases using subtype-selective ET receptor antagonists and ET_B receptor-deficient animals. Our studies have demonstrated that ET−1 overproduction and ET_A-mediated ET−1 actions seem to play a crucial role in the development of several types of hypertensive and post-ischemic diseases. On the other hand, ET−1 biosynthesis and release are regulated at the transcriptional level, and various endogenous substances are known to stimulate ET−1 gene expression by DNA binding of transcription factors. We and others have recently demonstrated that nuclear factor-κB (NF-κB), a transcription factor with a pivotal role in inducing genes involved in immune, inflammatory and stress responses, is responsible for endothelial ET−1 production. In *in vivo* studies, agents that can inhibit the NF-κB activation improved the development of ET−1-related cardiovascular diseases. Thus, NF-κB inhibition may be one of pertinent treatments in ET−1 related diseases.