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NEP, ACE and Homologues: The Pathophysiology of Membrane Metalloproteases

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ABSTRACT

The zinc metalloprotease, neprilysin (NEP), plays a role in the metabolism of cardiovascular, inflammatory and neuropeptides, including mitogenic peptides such as bombesin. In the cardiovascular system, NEP has a primary role in the inactivation of natriuretic peptides but also contributes to local metabolism of angiotensin, endothelins and bradykinin. Hence NEP is seen as a potential therapeutic target and drug development is facilitated by its recent structural solution. In prostate cancer, NEP is dramatically downregulated allowing mitogenic peptides to drive androgen-independent progression of the disease. NEP also contributes to the catabolism of the neurotoxic beta-amyloid peptide in Alzheimer's disease. Thus up- or downregulation of NEP activity critically affects peptide metabolism and can contribute to the pathophysiology of a number of diseases. The human genome contains seven NEP-like enzymes, including the endothelin converting enzymes (ECE) and aspects of their physiology and properties will be highlighted. We have also identified a novel human homologue of the zinc metalloprotease, angiotensin converting enzyme (ACE). This enzyme (ACEH) hydrolyses angiotensins I and II but not bradykinin and functions exclusively as a carboxypeptidase. Its localization and possible roles in regulation of the renin-angiotensin and other peptide systems will be described and compared with those of ACE itself.Abs text

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