

Neprilysin: Novel Target for the Treatment of Heart Disease

TECHNICAL FIELD

Therapeutic: Heart Disease (2006-0701)

BACKGROUND

The accumulation of amyloid beta-protein (A-beta) in tissues is a pathological hallmark of amyloidoses, including all forms of Alzheimer's disease (AD) and some forms of heart disease, such as amyloid-induced cardiomyopathy. Amyloid oligomers found in heart disease are similar to the toxic entities found in AD patients and in other amyloid-based diseases. These oligomers are present in cardiomyocytes derived from human heart-failure patients and in animal models of desmin-related cardiomyopathy. A-beta is produced continuously and its concentration is determined in part by the activities of several degradative enzymes, including neprilysin. Decreased activity of neprilysin due to genetic mutation, or age- or disease-related alterations in gene expression or proteolytic activity may increase the risk for amyloidoses. Conversely, increased expression of this enzyme may confer a protective effect.

Increasing A-beta degradation through transcriptional or pharmacological activation or gene therapy represents a therapeutic strategy for the treatment of AD, and these approaches are currently being evaluated in cell-culture and animal models. Regulation of neprilysin as a therapeutic target in amyloid-associated heart disease should be considered a relevant pathway to treat these types of cardiac diseases.



TECHNOLOGY

Neprilysin, an enzyme that is being studied as a potential treatment for neurodegenerative diseases due to its ability to clear amyloid deposits in neurons, may also be an effective target for treating heart disease. By causing the cardiomyocyte-specific overexpression and accumulation of toxic pre-amyloid oligomers, which are normally degraded by neprilysin, an animal model of heart failure has been generated. The lab has also demonstrated that while normal human cardiomyocytes do not contain these oligomeric accumulations, there exists a diverse accumulation of the toxic oligomers in adult and pediatric patients with heart disease. Ectopic expression of amyloidogenic proteins in mice causes accumulation of these pre-amyloid oligomers and toxicity to cardiomyocytes, resulting in heart disease and cardiac death. In light of existing experimental evidence to suggest that exercise reduces amyloid deposits in animal models of Alzheimer's disease, Dr. Robbins' laboratory studied the effect of exercise on pre-amyloid oligomer levels and life expectancy. These studies revealed an increase in life expectancy and decrease in toxic oligomers, as well as other markers of cardiac pathology and apoptosis, in exercised animals. Neprilysin levels were shown to be significantly reduced in diseased mice, but increased to almost normal levels in exercised diseased mice. Therefore, it is possible that the interference with pre-amyloid oligomer accumulation in cardiomyocytes, possibly via an increase in neprilysin activity, is a potential treatment for cardiovascular disease.

APPLICATIONS

1. Potential therapy for heart disease
2. Research Tool

ADVANTAGES

- Potential to develop new therapeutic market

INVESTIGATOR

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STATUS

Patent applications pending.

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Neprilysin: Novel Target for the Treatment of Heart Disease

THE INVENTOR

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BACKGROUND

Dr. Robbin's research focuses on modeling human cardiovascular disease, particularly those diseases that result in compromised cardiac function.

The heart is fundamentally a multi-chambered pump, and there is a well-defined set of proteins that underlie its normal function. These proteins make up the contractile apparatus, which is responsible for the heartbeat, and it has been discovered that mutations in these proteins can cause cardiovascular disease. This type of disease is a major killer in the young adult population.



Although we understand the genetic basis of the disease, we do not fully comprehend how these mutations cause cardiac pathology to develop. Dr. Robbin's group creates mouse and rabbit models of these human diseases using transgenesis and gene targeting. Once the animals are created, the pathogenic processes can be studied under controlled conditions over the lifetime of the animal. As we begin to understand the disease's progression more clearly, we hope to identify legitimate therapeutic targets, which may delay or even prevent development of cardiac pathology.