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"TRPV1 is a component of the atrial natriuretic signaling complex, and using orally delivered antagonists, presents a valid therapeutic target in the longitudinal reversal and treatment of cardiac hypertrophy and heart failure"

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ABSTRACT

Activation of the atrial natriuretic signaling pathway is intrinsic to the pathological responses associated with a range of cardiovascular diseases that stress the heart, especially those involved in sustained cardiac pressure overload which induces hypertrophy and the pathological remodeling that frequently leads to heart failure. We identify transient receptor potential cation channel, subfamily V, member 1, as a regulated molecular component, and therapeutic target of this signaling system. Data show that TRPV1 is a physical component of the natriuretic peptide A, cGMP, PKG signaling complex, interacting with the Natriuretic Peptide Receptor 1 (NPR1), and upon binding its ligand, Natriuretic Peptide A (NPPA, ANP) TRPV1 activation is subsequently suppressed through production of cGMP and PKG mediated phosphorylation of the TRPV1 channel. Further, inhibition of TRPV1, with orally delivered drugs, suppresses chamber and myocyte hypertrophy, and can longitudinally improve in vivo heart function in mice exposed to chronic pressure overload induced by transverse aortic constriction, reversing pre-established hypertrophy induced by pressure load while restoring chamber function. TRPV1 is a physical and regulated component of the natriuretic peptide signaling system, and TRPV1 inhibition may provide a new treatment strategy for treating, and reversing the loss of function associated with cardiac hypertrophy and heart failure.

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Introduction

Heart failure prevalence is in excess of 22 million cases worldwide, with an incidence of two million new cases a year. In the United states alone, 670,000 new cases of heart failure are diagnosed each year. Heart failure is the fastest-growing clinical cardiac disease burden in the United States, affecting 2% of the population, accounting for 34% of cardiovascular-related deaths, and representing 1–2% (~$40 billion) of all health care expenditures. Fourteen percent of the Medicare population has HF but they take up a disproportionate amount of Medicare dollars using ~43% of Medicare expenditures [1–6].

Heart failure is a condition that results from the heart's inability to maintain sufficient cardiac output to meet the metabolic demands of the body. It can be acute or chronic in nature, it can affect either side of the heart and it can be systolic or diastolic. Persistent cardiac pressure overload induces hypertrophy and pathological tissue remodeling, which leads to loss of heart function and often heart failure and death. The progression of cardiac hypertrophy represents the principal risk factor for the development of heart failure and subsequent cardiac death [2]. Cardiac hypertrophy is classically considered to be an adaptive and compensatory response that increases the work output of cardiomyocytes and thus maintains

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Supplemental data for this article can be accessed here.