REVIEW ARTICLE

Targeting TRPV1 and TRPV2 for potential therapeutic interventions in cardiovascular disease

NATHAN ROBBINS, SHERYL E. KOCH, and JACK RUBINSTEIN

CINCINNATI, OHIO

Cardiovascular disease is a leading cause of morbidity and mortality worldwide, encompassing a variety of cardiac and vascular conditions. Transient receptor potential vanilloid (TRPV) channels, specifically TRPV type 1 (TRPV1) and TRPV type 2 (TRPV2), are relatively recently described channels found throughout the body including within and around the cardiovascular system. They are activated by a variety of stimuli including high temperatures, stretch, and pharmacologic and endogenous ligands. The TRPV1 channel has been found to be an important player in the pathway of the detection of chest pain after myocardial injury. Activation of peripheral TRPV1 via painful stimuli or capsaicin has been shown to have cardioprotective effects, whereas genetic abrogation of TRPV1 results in increased myocardial damage after ischemia and reperfusion injury in comparison to wild-type mice. Furthermore, blood pressure changes have been noted upon TRPV1 stimulation. Similarly, the TRPV2 channel has also been associated with changes in blood pressure and cardiac function depending on how and where the channel is activated. Interestingly, overexpression of TRPV2 channels in the heart induces dystrophic cardiomyopathy; however, stimulation under physiologic conditions leads to improved cardiac function. Probenecid, a TRPV2 agonist, has been studied as a model therapy for its inotropic effects and potential use in the treatment of cardiomyopathy. In this review, we present an up to date account of the growing evidence that supports the study of TRPV1 and TRPV2 channels as targets for therapeutic agents of cardiovascular diseases. (Translational Research 2013;161:469–476)

Abbreviations: CGRP = calcitonin-gene regulated peptide; DMD = Duchenne muscular dystrophy; DRG = dorsal root ganglia; FDA = Food and Drug Administration; TRPV = transient receptor potential vanilloid; TRPV1 = transient receptor potential vanilloid type 1; TRPV2 = transient receptor potential vanilloid type 2; WT = wild-type

Cardiovascular diseases encompass the vast majority of comorbidities that contribute to millions of hospitalizations and deaths worldwide each year. Significant strides have been made in the management, treatment, and prevention of diseases such as hypertension, coronary artery disease, ischemic heart disease, and cardiomyopathy though the management for many of these is still not optimal and,

From the Department of Internal Medicine, Division of Cardiovascular Diseases, University of Cincinnati, Cincinnati, Ohio.

Conflict of interests: All authors have read the journal's policy on disclosure of potential conflicts of interest and have no conflicts of interest to disclose.

Submitted for publication November 21, 2012; revision submitted February 1, 2013; accepted for publication February 5, 2013.

Reprint requests: Jack Rubinstein, MD, Department of Internal Medicine, Division of Cardiovascular Diseases, University of Cincinnati, 231 Albert Sabin Way, Cincinnati, OH 45267-0542; e-mail: rubinsjk@ucmail.uc.edu.

1931-5244/$ - see front matter

Published by Mosby, Inc.

http://dx.doi.org/10.1016/j.trsl.2013.02.003

therefore, the development of new therapies is warranted. This review proposes 2 proteins, transient receptor potential vanilloid type 1 and 2 (TRPV1 and TRPV2), as potential therapeutic targets to treat an array of cardiovascular diseases and subsequently describes several agonists as model therapeutic agents.

BACKGROUND

Transient receptor potential channels are a diverse group of proteins conserved in many species of mammals and are divided into 7 subgroups, one of which is the transient receptor potential vanilloid (TRPV) subgroup.[1] The TRPV1 channel, also known as the vanilloid receptor and the capsaicin receptor, was the first discovered TRPV channel and is the best studied of the group.[2] Shortly after the discovery of TRPV1, another channel with close resemblance was discovered and found to share 86.2% homology with approximately 760 amino acids being the same, as shown in Fig 1. This closely related protein was appropriately named vanilloid receptor like channel, subsequently called growth factor regulated channel and more recently TRPV2.[3] Both TRPV1 and TRPV2 are found within and around the cardiovascular system and are activated by high temperatures and specific endogenous and pharmacologic agonists. The TRPV1 channel is localized in the sensory nerves surround cardiovascular structures,[2] near the epicardial surface of the heart,[4] and in vascular endothelial cells which line the vessels of the cardiovascular system.[5] Many factors activate TRPV1 including temperatures greater than 43°C,[2] pH values less than 5.9[6] and molecules including capsaicin,[2] free oxygen radicals,[7] 12-lipoxygenase (12-LOX)[8] 20-hydroxyeicosatetraenoic acid,[9] and cannabinoids such as anandamide.[10] Bradykinin has also been found to mediate TRPV1 by decreasing its threshold temperature for heat activation,[7] however, it does not appear to directly activate TRPV1.[11] Similarly to TRPV1, TRPV2 channels are located within the dorsal root ganglia[3] as well as aortic smooth muscle cells,[12] intralobar pulmonary arteries,[13] and cardiomyocytes.[14] TRPV2 channels are activated by higher temperatures, greater than 52°C, compared with TRPV1.[3] In addition to heat, TRPV2 channels are activated mechanically via cell stretch[12] and chemically by such substances as insulin-like growth factor 1[15] and probenecid.[16]

Activation of TRPV1 and TRPV2 channels lead to increased intracellular calcium levels and various cellular responses,[2,3] throughout the body. For example, TRPV1 channels in C-fibers are essential for autonomic reflexes and sensations such as coughing[17] and itch,[18] and some of these cellular responses are directly related to the cardiovascular system. The TRPV1 channel has been found to be a molecular target for substances released after an ischemic event and when activated after a myocardial infarction leads to the sensation of chest pain.[19] This sensation has been linked to cardioprotection via TRPV1 by a series of elegant experiments by Jones et al, which demonstrated that peripheral nociception elicits cardioprotection in wild-type (WT) mice.[20] Wang et al, working independently, found that genetic abrogation of TRPV1 results in a larger infarct size, presumably as a consequence of the absence of pain sensation and, therefore, through lack of pain induced ischemic preconditioning.[21]

Both, TRPV1 and TRPV2 have been linked to cardiopulmonary and systemic vasoactive responses via chemical[10,22] and mechanical stimuli.[12,23] Activation of over-expressed TRPV2 in cardiomyocytes can be detrimental,[12] however, under normal physiological conditions, activation can lead to improved function.[24] All of these processes are important in the cardiovascular system and involve TRPV1 and TRPV2, which make them ideal targets for therapeutic agents of cardiovascular disease.

CHEST PAIN

A critically important symptom of myocardial ischemia during an infarction is chest pain. Though the molecular cascade surrounding pain perception during an acute coronary event has yet to be clarified, several hypotheses have been able to partially explain the association of chest pain with damaged myocardium. Additional mechanisms are continuously being proposed to more completely understand the relationship, and 1 such mechanism proposes that TRPV1 functions as a molecular sensor upon activation as shown in Fig 2 *A*.

During a myocardial infarction, the limitation of blood flow through a coronary artery results in downstream tissue hypoxia and release of chemical messengers such as bradykinin,[25] free oxygen radicals,[7] and protons.[26] Investigators have proven the latter 2 of these chemicals directly activate TRPV1. Application of hydrogen peroxide, a source of free oxygen radicals, was found to increase afferent sympathetic nerve fiber activity.[27] Similar experiments, shortly thereafter, noted this effect was abrogated when pretreated with a TRPV1 antagonist verifying TRPV1's pivotal role in this cascade.[7] Additionally, in vitro experiments demonstrate a dose dependent increase in current when TRPV1 transfected mammalian cells and xenopus oocytes are treated with protons.[26]

In a set of experiments conducted by Zahner et al,[4] TRPV1 was investigated in a myocardial ischemia model to further understand the cause of chest pain.