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Ion channels, transporters, and pumps as targets for heart failure

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Abstract

Congestive heart failure (CHF) is a leading cause of morbidity and mortality. CHF is marked by atrial and ventricular enlargement and reduced cardiac contractility, as well as an association with an increased incidence of atrial and ventricular arrhythmias and sudden cardiac death. Dysfunctional ion channel function is one of the major underlying mechanisms of the reduced contractility and arrhythmias. In this review, we explore the utility of ion channels, as well as transporters and pumps, as targets for treatment of heart failure, focusing predominantly on treatment for reduced contractility and arrhythmias.

Keywords

heart failure; ion channels; transporters; pumps; treatment; arrhythmias

Introduction

Heart failure is a major cause of hospitalizations and death. Despite significant basic research and clinical trials, progress in improving overall outcomes has been limited. The prognosis for patients with heart failure is limited; over 15% die within one year of diagnosis and up to 80% die within six years [1]. Many of these deaths are likely due to an arrhythmia.

Congestive heart failure (CHF) is a complex syndrome, marked by reduced cardiac contractility and blunted adrenergic responsiveness. In an attempt to compensate for reduced cardiac output, the sympathetic nervous system and renin-angiotensin-aldosterone systems are activated, which eventually becomes maladaptive and leads to further heart failure progression. The cellular and molecular mechanisms are the subject of intense investigation, and some controversy exists in the field. For many years, research and treatments have focused on increasing cardiac contractility, in many cases by stimulating adrenergic pathways with agents such as β -adrenergic agonists and or phosphodiesterase inhibitors [2]. These agents increase cyclic adenosine monophosphate (cAMP) levels in cardiomyocytes, leading to protein kinase A (PKA) phosphorylation of proteins responsible for excitation-contraction coupling in the heart. Although these agents can acutely increase contractility, their side-effects, including increasing risk for arrhythmias and sudden cardiac death, preclude long-term use.

Ventricular arrhythmias are frequently the cause of sudden death in heart failure patients. The action potential is the key determinant of cardiac electrical activity in the heart. Ion channel

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remodeling with prolongation of the action potential has been clearly shown in numerous studies [3]. Decreased outward current or an increase in inward current during the plateau phase of the action potential are important causes of the increase in action potential duration.

In failing hearts, there are many reports demonstrating dysfunctional regulation of intracellular sodium (Na^+) [4,5]. Downregulation of potassium (K^+) channels has also been shown in heart failure [6,7]. Moreover, calcium (Ca^{2+}) cycling defects play important roles in heart failure-induced dysfunction as well. Ion channels, transporters, and pumps of all these cations are currently being explored as targets for therapy. Although kinases and phosphatases, which potentially regulate ion channels, are also novel and potentially important targets for CHF treatment, we will focus this review on targeting a few key ion channels, transporters, and pumps directly through the application of novel small molecules and gene approaches.

Ca^{2+} cycling defects in heart failure

Ca^{2+} plays a critical role in mediating excitation-contraction coupling. Cardiomyocytes control Ca^{2+} through elaborate mechanisms designed to permit contraction, relaxation and autonomic control (Fig. 1). Membrane depolarization triggers Ca^{2+} influx through the L-type Ca^{2+} channels. This influx leads to activation of the ryanodine receptor (RyR), positioned in the sarcoplasmic reticulum membrane [8].

RyR is an essential component of excitation-contraction (E-C) coupling in skeletal and cardiac muscle, functioning as the sarcoplasmic reticulum (SR) Ca^{2+} release channel. Several modulatory elements are bound to it, including FK506 binding protein, a member of the immunophilin family of cis-trans peptidyl-prolyl isomerases [9] (FKBP12 in skeletal muscle [10] and FKBP12.6 in cardiac muscle [11,12]), PKA and its anchoring protein, muscle A kinase anchoring protein (mAKAP), protein phosphatase 1 (PP1) and protein phosphatase 2a (PP2A) [13]. The recruitment of the kinase(s) and phosphatases into the complex is mediated through specific leucine zipper interactions on the anchoring proteins and RyR. The released Ca^{2+} binds to thin filament troponin C, which then permits contractile interactions between actin and myosin. RyRs are then inactivated, in part due to depletion of intra-SR Ca^{2+} and coupling gating [14]. Ca^{2+} is pumped back into the SR by the sarco(endo)plasmic reticulum Ca^{2+} -ATPase 2a (SERCA2a), or pumped out of the cell by the sarcolemmal $\text{Na}^+/\text{Ca}^{2+}$ exchanger (NCX) [15]. SERCA2a is modulated by the inhibitory protein, phospholamban (PLN).

Ca^{2+} regulatory proteins are phosphorylated by several kinases, including PKA and Ca^{2+} /calmodulin-dependent protein kinase II (CaMKII) [15]. PKA phosphorylates the L-type Ca^{2+} channel ($\text{Ca}_v1.2$), RyR and PLN. β -adrenergic receptor stimulation increases Ca^{2+} current, significantly affecting contractility, heart rate and amplitude of the cardiac action potential [16]. PKA phosphorylation of $\text{Ca}_v1.2$ causes a negative shift in the voltage dependence, increases probability of channel opening (P_o) and alters inactivation [16]. CaMKII phosphorylates and activates $\text{Ca}_v1.2$ through a process termed facilitation [17–19]. PKA and CaMKII increases RyR activity by phosphorylating S2808 and S2814 respectively [13,20]. Likewise PKA and CaMKII phosphorylate PLN [21,22].

Failing ventricular myocytes exhibit impaired contractility and abnormal Ca^{2+} transients, marked by a reduction in Ca^{2+} transient amplitude, an increase in diastolic Ca^{2+} concentrations and a slowed rate of diastolic Ca^{2+} transient decay [23,24]. Overall, cardiomyocytes demonstrate reduced SR Ca^{2+} content and a lower excitation-contraction coupling gain [25, 26]. SR Ca^{2+} load may be decreased because of reduced SERCA2a function, increased Ca^{2+} extrusion by NCX, or SR Ca^{2+} leak. Several groups have shown CHF-induced changes in the phosphorylation and/or function of specific Ca^{2+} handling proteins, which may account for some of these findings.

CHF-induced activation of the neurohormonal system leads to hyperphosphorylation of the RyR by PKA [13]. CHF-induced decreased association of phosphatases (PP1 and PP2A) [13] and a phosphodiesterase (PDE4D3) [27] with the RyR complex may also account for the increased phosphorylation of RyR. The increased phosphorylation at Ser²⁸⁰⁸ leads to dissociation of the regulatory protein, FKBP12.6 (also termed calstabin 2), which increases Ca²⁺ sensitivity and reduced channel closing, which may account for diastolic SR Ca²⁺ leak, contributing to heart failure progression. Using a S2808A knock-in mouse, Marks and colleagues demonstrated reduced HF progression after left-anterior descending artery ligation [28]. In contrast, Valdivia and colleagues reported that S2808A knock-in mice were not protected against hypertrophy-induced heart failure [29], although the control mice did not demonstrate significant heart failure, as evidenced by lack of LV dilatation and relatively preserved LV function [30].

PLN, which is a phosphoprotein, functions to regulate SERCA2a in the SR of cardiac muscle [31]. As previously stated, SERCA2a pumps Ca²⁺ from the cytosol into the SR of cardiac muscle against a large concentration gradient by hydrolyzing ATP, which results in muscle relaxation [32]. PLN's own phosphorylation status determines its action [33]. In the dephosphorylated state, PLN acts as an inhibitory peptide of the SERCA2a pump of cardiac myocytes. The inhibition of SERCA2a is released through phosphorylation of PLN. Increased SERCA2a activity results in a larger SR Ca²⁺ load, which upon excitation causes increased SR Ca²⁺ release, and subsequently, an increase in myocardial contractility. As a result, both the lusitropy and inotropy are linked to SERCA2a activity [31].

The two primary pathways of PLN phosphorylation have been elucidated [21,22]. PKA phosphorylates PLN at residue Ser¹⁶. Elevated levels of cytosolic Ca²⁺ result in the activation of CaMKII, which phosphorylates the residue Thr¹⁷ of PLN. In contrast, dephosphorylation of PLN at these residues occurs mainly through PP1, which is the major phosphatase of the SR.

Both animal and human studies of heart failure demonstrated altered levels of SERCA2a and PLN expression. In a rat model of myocardial infarction with worsening congestive heart failure, there were decreased levels of SERCA2a mRNA and protein levels as compared to baseline [34]. Moreover, in a study of mongrel dogs with pacing induced heart failure, decreased activity of the SERCA 2a pump was shown [35]. In guinea pigs with heart failure as a result of thoracic aorta banding, PLN protein levels were decreased at onset of heart failure as compared to baseline [36]. In contrast to RyR hyperphosphorylation, PLN phosphorylation is reduced in CHF, leading to inhibition of SERCA2a activity [37].

Direct manipulation of both PLN and SERCA2a genes via transgenic animal models have shown that pathological Ca²⁺ handling results in heart failure. For example, in PLN overexpressing transgenic rabbits, cardiomyopathy invariably ensues [38]. In contrast, transgenic PLN knockout mice have a hyperdynamic condition in which cardiac performance is increased and the effect of β -adrenergic stimulation was blunted [39]. In SERCA2a overexpressing mice, there is also a hyperdynamic state with increased systolic pressure, and a sizable increase in Ca²⁺ transient amplitude and contractility [40]. On the other hand, SERCA2a heterozygous knockout mice have decreased Ca²⁺ uptake and decreased ventricular systolic pressure [41]. (Homozygous SERCA2a knockout mice exhibit embryonic lethality.)

In studies of human donor and failing heart tissue, SERCA2a mRNA levels are reduced in failing compared to non-failing hearts [42,43]. Moreover, SR Ca²⁺ uptake and SERCA2a activity was reduced in failing human myocardium [44,45]. Studies of PLN mRNA and protein levels in human heart failure reveal that it is either decreased or there is no significant change compared to normal [43,44]. However, SERCA2a protein levels have been shown to decrease

to a greater level than PLN protein levels in failing myocardium [46]. As a result, there is a decrease in SERCA2a expression with either no change or slight decrease in PLN expression, resulting in an increase in the PLN to SERCA2a ratio. It has been hypothesized that by altering the ratio through inhibiting PLN or increasing SERCA activity in heart failure, it may be possible to improve Ca^{2+} handling [46].

Calcium cycling defects as therapeutic targets in heart failure

β -adrenergic blockers have been shown to have profoundly favorable effects on cardiac function and mortality in heart failure [47,48]. Although the molecular targets have been completely identified, one target may be the hyperphosphorylation of RyR. β -blockers have been shown to reduce the phosphorylation of the channel and restore normal function [49]. The 1, 4-benzothiazepine derivative JTV519 has been shown to improve cardiac function in a dog model of heart failure [50,51] and in the LAD-ligation mouse model of heart failure [52]. The molecular mechanism is through an allosteric conformational change in RyR that enhances rebinding of FKBP12.6 to the channel complex. This drug is also able to suppress ventricular arrhythmias [53]. These findings suggest that JTV519 and its derivatives may represent a new class of drugs for the treatment for heart failure.

Over-expressing SERCA2a using adenoviral vectors or adeno-associated viral (AAV) vectors has been shown in animal models to significantly improve cardiac function and attenuate CHF progression, reduce frequency of arrhythmias and improve survival [54–56] (Fig. 1). These results have led to two clinical phase I trials exploring the utility of over-expression SERCA2a in human heart failure. In one trial, heart failure patients will receive intracoronary delivery of AAV1-SERCA2a [57]. The other phase I trial will deliver AAV6-SERCA2a to patients undergoing implantation of a left ventricular assist device with the primary goals of assessing safety and biological effects [58]. The results are eagerly awaited.

Dysregulation of intracellular Na^+ regulation in CHF

Contractile dysfunction in human CHF is associated with increased $[\text{Na}^+]_i$, particularly the late Na^+ current (Fig. 1). There is a significant increase in the fraction of Na^+ channels that fail to enter an inactivated state resulting in a small, persistent Na^+ current during the action potential plateau, which is similar to a form of long QT syndrome (LQT3). Recent studies have identified that a major component of the late Na^+ current is $\text{Na}_v1.5$ [59]. As a result, both $\text{Na}_v1.5$ and the late Na^+ current represent novel potential targets for cardioprotection.

Acute intravenous infusion of ranolazine, which is an inhibitor of the late Na^+ current and an anti-ischemic/anti-angina drug, has been shown to improve left ventricular ejection fraction without a concomitant increase in myocardial oxygen consumption in dogs with chronic heart failure [60]. Ranolazine was also studied alone and in combination with metoprolol or enalapril for 3 months on LV function and remodeling in dogs with with microembolization-induced heart failure. Ranolazine prevented progressive LV dysfunction and global and cellular myocardial remodeling, and ranolazine in combination with enalapril or metoprolol improved LV function beyond that observed with ranolazine alone [61].

The Na^+/H^+ exchanger (NHE), which is ubiquitously expressed in mammalian cells and electroneutrally exchanges intracellular H^+ for extracellular Na^+ to regulate intracellular pH and intracellular Na^+ , represents another target for treatment of heart failure [62] (Fig. 1). Nine exchanger isoforms have been identified. NHE-1 is the cardiac-specific isoform. The inward gradient produced by the Na^+/K^+ ATPase provides a constant driving force for NHE-mediated H^+ extrusion and Na^+ influx. NHE-1 activity is increased by reactive oxygen species, intracellular acidosis or stimulation of G protein-coupled receptors with angiotensin II, endothelin, and $\alpha 1$ adrenergic agonists [63]. Increased NHE-1 activity causes increased

intracellular Na^+ , which leads to Ca^{2+} overload through the $\text{Na}^+/\text{Ca}^{2+}$ exchanger, myocardial dysfunction, hypertrophy, apoptosis and failure. Heart failure is associated with an increase in $[\text{Na}^+]_i$ caused in part by increased NHE-1 dependent Na^+ influx leading to $\text{Na}^+/\text{Ca}^{2+}$ exchanger mediated increase in $[\text{Ca}^{2+}]_i$ [4,64,65].

Inhibition of NHE-1 activity leads to beneficial effects in ischemia/reperfusion injury in mice. In two large clinical trials (Guard During Ischemia against necrosis (Guardian) and Evaluation of the safety and cardioprotective effects of eniporide in acute myocardial infarction (ESCAMI)), no overall benefit was detected with NHE-1 inhibition [66,67]. In the Sodium-Hydrogen Exchange Inhibition to Prevent Coronary Events in Acute Cardiac Conditions (EXPEDITION) Study, cariporide treatment was associated with myocardial benefits in patients with ischemic heart disease, but was surprisingly associated with significantly greater (but small) incidence of strokes [68]. The adverse effect of cariporide was found in a subgroup of patients following coronary artery bypass graft surgery, but not in patients with CHF. Further studies are still needed to study the efficacy of NHE-1 as a viable target for heart failure.

K⁺ channels as targets for treatment of CHF

Changes in cardiac K^+ channel expression and function are well-known in CHF. The transient outward current (I_{to}), which is partly mediated by the K^+ channels $\text{K}_{\text{v}4.2}$ and $\text{K}_{\text{v}4.3}$, plays an important role in the early portion of repolarization and may contribute to phase 2 re-entry [69,70] (Fig. 1). Functional down-regulation of I_{to} with resultant action potential prolongation is one of the most consistent changes in ion channel activity in heart failure [71]. I_{to} blockade with the bradycardic agent, tedisamil, has been shown to be protective against animal models of ventricular arrhythmias, atrial flutter, and ischemia-reperfusion related arrhythmias [72, 73]. However, in patients with congestive heart failure due to dilated cardiomyopathy, tedisamil resulted in decreased heart rate with an increase in blood pressure [74]. While tedisamil may not be ideal for CHF patients, further methods of I_{to} modulation are still actively being pursued.

Other K^+ channels under investigation are mitochondrial ATP-sensitive K^+ channels ($\text{mitoK}_{\text{ATP}}$). Given the integral role of mitochondria in either the enhancement or suppression of cell death, these ion channels are of particular importance. Activation of $\text{mitoK}_{\text{ATP}}$ prevents lethal ischemic injury *in vivo*, suggesting that these channels are important for ischemic preconditioning. Pharmacological opening of $\text{mitoK}_{\text{ATP}}$ channels by diazoxide has been shown to preserve mitochondrial integrity and suppressed apoptosis in cultured rat neonatal cardiac ventricular myocytes [75]. The demonstration that diazoxide can thwart or reduce myocyte apoptosis via the activation of $\text{mitoK}_{\text{ATP}}$ channels provides a putative mechanism whereby this agent might protect cardiac myocytes during episodes of acute heart failure.

In general, K_{ATP} channels serve as metabolic sensors, adjusting membrane excitability to match cellular energetic demand. In the heart, K_{ATP} channels are typically closed, but open in response to cardiac stress including ischemia, physical exertion and stress hormones [76], shortening the action potential. Genetic deletion of K_{ATP} channels (knockout of Kir6.2 subunit) produced defective cardiac action potential shortening, predisposing to early afterdepolarizations and ventricular dysrhythmias [77]. The knockout mice also developed biventricular CHF within hours of aortic constriction, which was not observed in wild-type mice. Surviving knockout mice exhibited compromised cardiac function and myocardial hypertrophy [78]. Thus, cardiac K_{ATP} channels are protective against left ventricular pressure overload and CHF. This work raises the question of whether K_{ATP} channel openers might be useful in treatment of CHF [79]. These openers are chemically heterogeneous and include as different classes as the benzopyrans, cyanoguanidines, thioformamides, thiadiazines, pyridyl nitrates, cyclobutenediones, dihydropyridine related structures, and tertiary carbinols [80].

Summary

The development of heart failure is associated with changes in a myriad of structural, signaling, regulatory, and metabolic proteins. Ion channels, transporters, and pumps are only a subset of proteins that are altered during heart failure. However, as important regulators of membrane excitability and contractility, they remain key targets in mitigating and/or potentially reversing heart failure. Pathologic handling of Ca^{2+} , Na^{+} , and K^{+} has been consistently and uniformly shown to result in decreased cardiac contractility and increased incidence of arrhythmias. As a result, modulation of these proteins is of particular importance.

Along with a better understanding of the molecular and genetic basis of heart failure, the emergence and growth of translational cardiovascular research has allowed for the development of pharmacologic agents and gene therapy. Current translational research with treatments targeted towards ion channels has shown considerable benefits in animal models, particularly in regards to Ca^{2+} and Na^{+} handling. These favorable results have given way to several clinical trials. The results from the clinical trials will be eagerly awaited.

It is important to note, however, that while great strides in developing therapeutic agents have been made, excitement should be tempered. Many of the agents developed are far from ideal, with either narrow therapeutic windows or low efficacy. As a result, there is still an urgent and pressing need to discover novel and improved therapeutic strategies.

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Figure 1.
Ion channels implicated in heart failure and the therapeutic agents utilized to modulate them. An "X" denotes that a compound inhibits the channel it overlies.