Sodium Ion Transporters as New Therapeutic Targets in Heart Failure

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Abstract: Sodium ion transporters in sarcolemma are involved in numerous vital cell functions, such as excitability, excitation-contraction coupling, energy metabolism, pH and volume regulation, development and growth. In a number of cardiac pathologies, the intracellular sodium concentration ([Na⁺]) is elevated. Since [Na⁺] and intracellular Ca²⁺ concentration ([Ca²⁺]) are coupled through the Na⁺/Ca²⁺-exchanger, these cardiac pathologies display disturbed calcium handling. For instance, [Na⁺], is increased in heart failure (HF) leading to Na⁺/Ca²⁺-exchanger mediated increase in [Ca²⁺], reduced contractility and increased propensity to arrhythmias. Several studies support the contention that an increase in [Na⁺], and [Ca²⁺], transduces a signal the nucleus, that triggers development of cardiac remodelling and hypertrophy. Pharmacological intervention, which favourably interferes with [Na⁺], and [Ca²⁺], homeostasis, might prevent hypertrophy, cardiac remodelling, arrhythmias and HF. The most important sodium transport mechanisms that may underlie increased [Na⁺], are: Na⁺/H⁺-exchanger (NHE-1), Na⁺-HCO₃⁻ co-transporter (NBC), Na⁺-K⁺-Cl⁻ co-transporter (NKCC), Na⁺-channel, Na⁺/K⁺-ATPase and Na⁺/Ca²⁺-exchanger (NCX).

Preclinical studies showed that pharmacological interventions, targeted against sarcolemmal sodium ion transporters, proved effective in ameliorating heart failure. In this respect: 1) NHE-1 inhibition reduces cardiac remodelling, hypertrophy and HF, although, in the patients following coronary artery bypass graft surgery, it was associated with an increase of stroke. 2) The activity of NBC is up-regulated, during the development of hypertrophy and may be a therapeutic strategy to prevent the development of hypertrophy and HF. 3) NKCC is increased in post-infarction HF, and the inhibition of NKCC attenuated post-infarction remodelling. 4) Inactivation of sodium channels is impaired in HF, which may result, in increased Na⁺ influx and prolongation of the action potential. 5) Blockade of NCX may be useful as a part of a combined therapeutic approach. Inhibition of reversed mode, or activation of forward mode NCX reduce Ca²⁺ overload. 6) Inhibition of Na⁺/K⁺-ATPase (digoxin), is used to increase contractility, however, it enhances progression of HF. Oppositely, new drugs which increase activity of Na⁺/K⁺-ATPase may prevent the development of cardiac remodelling hypertrophy and HF.

In this review we give an overview and discuss the therapeutic relevance of the different sodium ion transport mechanisms in the setting of heart failure.

INTRODUCTION

The incidence and prevalence of heart failure (HF) have increased over the last decades. The main reasons for this increase are the ageing population and an increase in survival rate after myocardial infarction and other cardiovascular diseases. Although, pharmacotherapy has significantly improved survival, the prognosis of HF is still rather poor. Total mortality is high and approximately half of the deaths are sudden and unexpected. Angiotensin-converting-enzyme (ACE)-inhibitors generally given with diuretics, is the standard treatment for patients with HF, whereas, beta-adrenergic receptor antagonists (β-blockers) and Na/K-pump inhibitors (digoxin) are given to respectively prevent arrhythmias and improve contractility. Despite and improvement in the therapy, mortality in heart failure (HF) remains high and there is a need for alternative additional approaches [1, 2]. The major stimulus to initiate HF, is sustained increased workload of the heart, mostly due to the hypertension and/or myocardial infarction. The increased workload leads to hypertrophy and cellular and structural remodelling such as altered calcium handling [3, 4], excitation-contraction coupling [5], contractility [6], energy metabolism [7], cytoskeleton [8] and extracellular matrix [9]. Dysfunctional Ca²⁺ (disturbed Ca²⁺ handling) is characterized by reduced systolic Ca²⁺, increased diastolic Ca²⁺, elevated decay time of the Ca²⁺ transients, and decreased sarcoplasmic reticulum (SR) Ca²⁺ content [10-12] (see also Fig. 5). These alterations translate into functional incompetence of the heart with reduced fractional shortening, increased diastolic tension, relaxation abnormalities and arrhythmias. In addition increased intracellular calcium concentration ([Ca²⁺]) can directly accelerate protein synthesis [13-15] and activate critical hypertrophic pathways leading to altered gene expression (Fig. 1), such as mitogen-activated protein kinase (MAPKs) [16], calcineurin [17], Ca²⁺/calmodulin dependent kinase II (CaMKII), ezrin radixin moesin (ERM), phosphoinositide 3 kinase and the serine-threonine kinases (AKT) [18]. Although hypertrophy of the myocardium is
initially an adaptive response, prolonged hypertrophy is associated with increased sudden cardiac death and progression to HF [19-21].

Ca\(^{2+}\) regulation is closely linked to intracellular sodium handling ([Na\(^{+}\)], because the route for Ca\(^{2+}\) efflux from myocytes is via the Na\(^{+}/Ca^{2+}\)-exchanger (NCX). NCX utilize the electrochemical Na\(^{+}\) gradient to couple energetically unfavourable Ca\(^{2+}\) efflux from the myocytes to Na\(^{+}\) transport. NCX functions in the forward mode (Ca\(^{2+}\) efflux/Na\(^{+}\) influx), thereby reducing diastolic Ca\(^{2+}\) levels by extruding Ca\(^{2+}\). In addition, NCX can also function in reversed mode (Ca\(^{2+}\) influx/Na\(^{+}\) efflux) dependent on the sarcolemmal Na\(^{+}\) gradient. In animal models of HF and hypertrophy as well as in human heart failure, it has been shown that [Na\(^{+}\)] is increased [22-30]. When [Na\(^{+}\)] increases, NCX shifts to less forward and more reversed mode [22, 23] (see also Fig. 8), resulting in an increase of [Ca\(^{2+}\)] [22]. Changes in Na\(^{+}\) regulation will thus directly affect [Ca\(^{2+}\)] handling. Therefore, it can be argued that prevention of increased [Na\(^{+}\)], and the subsequent [Ca\(^{2+}\)] rise, may prove beneficial in the patients at risk to develop hypertrophy and HF. In steady state, Na\(^{+}\) homeostasis is the result of the balance between the influx and efflux of sodium ions. In cardiac myocytes Na\(^{+}\) efflux is primarily regulated by the Na\(^{+}/K^{+}\) ATPases with moderate contribution of NCX, whereas Na\(^{+}\) influx depends mainly on Na\(^{+}\)-channel and NHE-1 activity with minor contribution of other sodium transporters (Fig. 2). All these mechanisms are subject of regulation [31] and therefore can contribute to abnormal Na\(^{+}\) handling in the failing heart. The feature of this review is to discuss the therapeutic relevance of these sodium ion transporters in the treatment of HF.

THE Na\(^{+}/H^{+}\)-EXCHANGER

The Na\(^{+}/H^{+}\)-exchanger (NHE) is an integral membrane protein expressed in mammalian cells that becomes activated upon an intracellular acidosis. NHE expels one H\(^{+}\) from the cytoplasm in exchange with one extracellular Na\(^{+}\), until a near neutral intracellular pH is reached. At resting pH\(_{i}\) values of NHE are still active, however, perfectly balanced by the sarcolemmal acid loaders. The small overlap in acid extrusion and acid loading activity causes background NaCl loading. For this reason NHE has, besides pH\(_{i}\) regulation, also a major role in maintaining intracellular solute concentrations and cell volume regulation.

Until now 9 isoforms of the exchanger have been identified [32]. NHE-1 is the most ubiquitously expressed and the predominant isoform in the plasma membrane of the myocardium [33]. The activity of NHE-1 is regulated by e.g., stretch and neurohumoral factors that target membrane bound G-protein coupled receptors, such as catecholamines, angiotensin II and endothelin I. These factors, abundantly present in HF, stimulate their receptors and activate signalling transduction pathways that cause (de)phosphorylation and (un)binding of co-factors from the NHE-1 C-terminus [33-36].
In animal models and in the patients with HF, NHE-1 activity is proved to be significantly increased [24, 25, 37-41] (Fig. 3). It is expected that hyperactivity of NHE-1 is associated with a more alkaline pH and an elevated [Na⁺], However, in HF enhanced acid extrusion by NHE-1 is perfectly balanced by an equivalent increase in acid-loading through the Cl-/HCO₃⁻-exchanger (anion exchanger, AE), thereby leaving pH unchanged under bicarbonate buffered conditions [42, 43]. Regarding the simultaneous increase in NHE-1 and AE activity at resting pH values in HF, one can speculates that the actual [Na⁺] under bicarbonate-buffered conditions should be much higher as always measured under non-bicarbonate-buffered conditions (Fig. 4). Yet, experimental data on this in HF is lacking. Evidence exists that a long term increase in NHE-1 activity is harmful, due to its indirect effect on the [Ca²⁺]. Increased NHE-1 activity elevates [Na⁺] (Fig. 3) and subsequently causes a Ca²⁺ overload through NCX, which secondary leads to arrhythmias, myocardial dysfunction, hypertrophy, apoptosis and HF [44-48].

Consequently, inhibition of NHE-1 might be a therapeutic strategy to prevent the increase in [Na⁺], and [Ca²⁺], hypertrophy and the development of HF. In this respect, it has been shown in several studies that chronic inhibition of NHE-1 prevents and/or attenuates hypertrophy and the development of HF [27, 46, 49-56]. These studies showed that NHE-1 inhibition improves survival rate, reduces fibrosis and apoptosis, preserves contractility, and prevents ionic and electrical remodelling. In accordance, SR calcium handling and the amplitude of calcium transient are normalized in pressure-volume overloaded rabbits with HF, that were fed with a NHE-1 inhibitor “cariporide” containing diet (Fig. 5). From the prevention of excessive fibrosis, prolongation of action potential duration, and delayed after depolarizations [57-61], one can conclude that NHE-1 inhibition is also anti-arrhythmic. This anti-arrhythmogenic effect together with maintenance of contractility explains why the rate of survival is higher in HF following inhibition of NHE-1 [46, 49].

In most studies, in which chronic inhibition of NHE-1 has been applied experimentally, treatment started immediately after the induction of hypertrophy and HF. From a clinical point of view however, it is even more relevant to determine whether chronic inhibition of NHE-1 is capable to reverse signs of hypertrophy and HF, after it has already been developed. Indeed, NHE-1 inhibition treatment reduced hypertrophy in rats with myocardial infarction [50], and reversed hypertrophy and improved contractility in spontaneously hypertensive rats (SHR) (Fig. 6) [62]. Moreover, in rabbits with volume and pressure overload inhibition of NHE-1, not only reversed hypertrophy and reduced signs of HF but also reversed ionic and electrical remodelling [63] are found.

Unfortunately, in a clinical trial designed to prevent ischemia and reperfusion injury using cariporide to inhibit NHE-1 activation,
in the patients following coronary artery bypass graft surgery, adverse effects were demonstrated [64]. In cariporide treated patients an increase incidence of stroke was found. This halted further clinical studies on NHE-1 inhibitors as a cardio protective drug. More studies are required to find out whether different NHE-1 inhibitors or alternative strategies to inhibit NHE-1 activity will be efficient to treat and prevent the development of hypertrophy and HF in the patients without these adverse effects.

THE \textbf{Na}^+-HCO_3^- \textbf{COTRANSPORTER}

The \textbf{Na}^+-HCO_3^- cotransporter (NBC) is localized in sarcolemma and becomes activated upon intracellular acidosis. NBC transports extracellular \textbf{Na}^+ and HCO_3^- into the cytoplasm, thereby restoring the acidic pH_i to near neutral values. The relative contribution of NHE-1 and NBC in acid load recovery, is approximately 70% and 30%.

Mammalian hearts possess at least two different \textbf{Na}^+ dependent bicarbonate co-transporters, an electroneutral (1Na:1HCO_3^-) and an electrogenic NBC (1Na:2HCO_3^-) [45]. The human heart NBC (hhNBC) represents the electrogenic NBC (NBCe1) [65] whereas, NBCn1 is the cardiac electroneutral isoform [66]. The only function ascribed to NBC is its role in pH_i regulation; however, since it transports \textbf{Na}^+ into the cytoplasm it may also be important in cardiac \textbf{Na}^+ and Ca^{2+} homeostasis. In addition, activation of the electrogenic hhNBC may also affect the action potential configuration. Although, intracellular proton accumulation is possibly a major stimulus for the activation of NBC, the abundance of modulation sites on NBC also suggests a strong regulation of its activity by several intracellular signalling pathways [45]. Peptide hormones and catecholamines that act on the G-protein coupled receptors modulate NBC by shifting its set-point pH_i (pH_i at which an acid-base transporter is virtually quiescent) [47].

There are reports that NBCe1 plays a role in the development of ischemia/reperfusion injury in the heart [65]. Following reperfusion intracellular pH_i is quickly restored by NHE-1 and NBC at the expense of \textbf{Na}^+ influx. In the still energy-deprived tissue the \textbf{Na}^+/K^+ ATPase is not fully recovered and cannot compensate this \textbf{Na}^+ influx. Consequently, \textbf{[Na]}_i sharply rises and causes a NCX-mediated \textbf{Ca}^{2+} overload at the moment of reperfusion that leads to hypercontracture and lethal cell injury. Indeed, administration of anti-hhNBC antibody markedly protects systolic and diastolic functions of the heart during reperfusion. Yet, the role of NBCn1 in reperfusion injury remains controversial [43].

Recently, it has been shown in a cardiac hypertrophic rat model that the activity of both NBCn1 and NBCe1 are up-regulated [67]. In this rat model, it had been suggested that enhanced NBC activity provides a mechanism for \textbf{[Na]}_i overload in hypertrophied hearts. In contrast, in a pressure-volume overload rabbit model of HF no differences were observed in cardiac NBC activity [68]. Thus, whether or not NBC contributes to elevated \textbf{[Na]}_i, may depend on the species and on the specific pathological condition. In principal inhibition of NBC could be a new therapeutic strategy to prevent the increase in \textbf{[Na]}_i. However, it remains unknown whether inhibition of NBC actually prevents the elevation of \textbf{[Na]}_i, and the development of hypertrophy and HF. A complicating factor for these studies is the lack of specific NBC inhibitors.

THE \textbf{Na}^+-K^+\textbf{-2Cl}^- \textbf{COTRANSPORTER}

The \textbf{Na}^+-K^+\textbf{-Cl}^- cotransporter (NKCC) is localized in the sarcolemma and is involved in the cell volume regulation. NKCC transports extracellular \textbf{Na}^+ and \textbf{K}^+ and \textbf{Cl}^- ions into the cytoplasm with a stoichiometry of 1Na+:1K+:2Cl^-, thereby supplying the cell with solutes that may prevent cell shrinkage.

Cardiac hypertrophy was assessed by heart weight/ body weight ratio in 4 months old untreated SHR (bar); in 5 months old cariporide-treated SHR (dashed bar) and in 5 months old untreated SHR (grey bar). Reproduced with permission from ref 62

The NKCC1 is the most ubiquitous expressed isoform and is present in the heart. It has been demonstrated that NKCC can be modulated by adrenergic, angiotensin II, and aldosterone receptor stimulation [69]. Ligands for these receptors are abundantly present in HF and may increase NKCC activity.

NKCC has been shown to contribute to \textbf{Na}^+ loading during myocardial ischemia and reperfusion. Accordingly, the NKCC inhibitor bumetanide reduced \textbf{Na}^+ loading and attenuated ischemic injury in diabetic rats [70]. Moreover, recent evidence indicates that myocardial NKCC is increased in post-infarction HF [71]. Although, in this model of HF, NKCC inhibition attenuated post-infarction remodelling, it remains to be determined whether or not increased NKCC underlies elevated \textbf{[Na]}_i, in HF. If NKCC proves a major pathway for increased \textbf{Na}^+ influx in HF than classical loop diuretics, bumetanide and furosemide, may be useful therapeutic tool to prevent the development of hypertrophy and HF. It should be taken into account that these loop diuretics reduce volume...
overload by stimulating natriuresis and diuresis, which by itself, improves hemodynamics and may reduce hypertrophy and HF [72].

THE LATE Na⁺-CHANNEL CURRENT

Sodium channels (Na⁺-channels) are activated on the depolarization of sarcolemma. The Na⁺ current (I_{Na}) flowing through these channels, is responsible for the fast upstroke of the cardiac action potential (AP) and contributes to the fast conduction during cardiac excitation. Most of the current rapidly inactivates (I_{NaT}) within a few milliseconds upon depolarization, however, a small fraction of this current inactivates slowly, the so-called late sodium current (I_{NaL}) [73] (Fig. 7 panel A).

![Sodium current (nA)](image)

Fig. (7). Sodium current (I_{Na}) and increased variability of action potential duration in HF.

The late I_{Na} is associated with slow inactivation component of I_{Na}. Panel A illustrate a normal (left) and an increased late I_{Na} (right) due to impaired inactivation of the sodium current. The enhanced late I_{Na} is accompanied by delayed ventricular repolarization.

Panel B; shows action potential recorded by perforated patch clamp in representative normal and failing dog ventricular myocytes. Panel C shows that variability in beat-to-beat action potential duration in failing myocytes can be rescued by electrical neutralization of the late I_{Na}. Panel B and C. Reproduced with permission from ref 83.

The TTX-resistant Na⁺-channel Na(v)1.5 is predominantly expressed in the heart, whereas the minor part of the sodium channel is composed of the TTX-sensitive sodium channels Na(v)1.1, 1.2, 1.3, 1.4, 1.6 [74]. Electrophysiological recordings showed that TTX-resistant and TTX-sensitive Na⁺ channels, respectively, accounted for 92% and 8% of I_{Na} in adult ventricular cardiomyocytes [75]. The gating and kinetics of the sodium channel are largely controlled by the membrane voltage, however the channels can also be regulated by PKA and PKC [76], calcium, calmodulin and CaMKII [77].

Initial studies using whole-cell patch-clamp technique configuration, showed no change in I_{Na} in HF [78], although later studies showed a decrease in current density [79, 80]. In this respect, it must be realized that reduction of I_{NaT} can lead to slowing of the upstroke of the AP, reduced conduction velocity, unidirectional block and re-entrant arrhythmias [80]. However, the amount of Na⁺ influx will not be changed unless the amplitude of the upstroke of the AP is changed. Similar amplitude of the upstroke, fast or slow, requires an equal amount of Na⁺ entry albeit in a longer period of time. Therefore, reduction of I_{NaT} will not necessarily change [Na⁺], In several studies it has been shown that I_{Na} is increased in HF [81-84]. In contrast to I_{NaT} an increase of I_{NaL} results in prolongation of the AP duration (Fig. 7 panel B) and increased influx of Na⁺ ions. For that reason it has been suggested that increased [Na⁺] in HF is caused by an increase of I_{NaT} and that inhibition of I_{NaT} can prevent [Ca²⁺] overload and may be beneficial for the development of hypertrophy and HF [83, 85, 86]. Yet, no data are available in which inhibition of I_{NaT} proved beneficial in preventing the development of hypertrophy and HF or in reducing [Na⁺]. On the other hand, it has been shown that inhibition of I_{Na} can shorten AP duration and decrease the propensity to evoke EADs related arrhythmias (Fig. 7 panel C) [82-86] and improve mechanical efficiency [87]. Whether I_{Na} inhibition will be an effective treatment for hypertrophy and HF remains to be investigated.

THE Na⁺/Ca²⁺-EXCHANGER

The Na⁺/Ca²⁺-exchanger (NCX), a surface membrane antiporter, is the primary pathway for Ca²⁺ efflux. The driving force of NCX depends on the sarcolemmal Na⁺ and Ca²⁺ gradient and the membrane voltage. NCX catalyzes the electrogenic transport of one Ca²⁺ ion across the membrane in exchange for three Na⁺ ions in a reversible manner, depending on its direction. By convention NCX-mediated transport is called ‘forward’ when Na⁺ is transported inward and Ca²⁺ outward and ‘reversed’, when ions are transported in the opposite directions.

The cardiac specific isoform NCX1 is abundantly present in the sarcolemma of cardiac myocytes. The large cytoplasmic loop of NCX is believed to contain the regulatory sites of the protein. Regulation is achieved by a variety of extracellular and intracellular factors. However, the exact mechanisms are not completely understood and require further investigation [31, 88-90].

In hypertrophy and HF it has been shown that NCX expression, activity and driving force is altered [23, 24, 91-97] and therefore could play a role in the impairment of Ca²⁺- and Na⁺ handling, altered contractility and arrhythmogenesis [88, 98-100]. It has to be realized, because of the steady-state consideration, that NCX-mediated Ca²⁺ efflux is equal to the L-type calcium channel mediated Ca²⁺ influx. L-type calcium current in HF proved unchanged or even reduced [101-107]. Thus regarding steady-state consideration, the Ca²⁺ and Na⁺ flux through NCX in HF is most likely not different from the ‘normal’ and thus cannot contribute to enhanced Na⁺ influx and altered Na⁺ handling observed in HF. On the other hand, it is known that the driving force of NCX is shifted to less forward mode, and increased reversed mode largely caused by an increase of [Na⁺] [23, 24] (Fig. 8). This results in an increase of cytosolic Ca²⁺ [24], to compensate for the shift in driving force, until the Ca²⁺ efflux through NCX equals the Ca²⁺ influx.

KB-R7943 and SEA-0400 are inhibitors of NCX [89,107], KB-R7943 largely affects the reverse mode of NCX [107], whereas SEA-0400 has no preference for forward or reversed mode. Inhibition of the forward mode reduces Ca²⁺ efflux and increases [Ca²⁺], which may ultimately activate hypertrophic signalling pathways (Fig. 1) and the development of HF. In addition, the increased [Ca²⁺], promotes sarcomplasmic reticulum (SR) Ca²⁺ loading and SR Ca²⁺ release, which render the myocytes more
Dynamic change of $\Delta G_{\text{ATP}}$ in 2 Hz stimulated myocytes isolated from control rabbits and rabbits with volume and pressure overload induced HF. Dotted area corresponds to reversed mode operation of NCX.

NCX mediated elevation of $[\text{Ca}^{2+}]_i$, which is known to be a pathological signal in the setting of HF. Inhibition of the pump results in a further increase of $[\text{Na}^+]_i$ and $[\text{Ca}^{2+}]_i$. In this respect it has been shown that inhibition of NCX promotes cardiac hypertrophy [130, 131].

The long term effect might be detrimental because of the increase in $[\text{Na}^+]_i$ and $[\text{Ca}^{2+}]_i$. In this respect it has been shown that inhibition of Na/K-pump reduces influx of Ca$^{2+}$ and may prevent $[\text{Ca}^{2+}]_i$ overload, which could reduce activation of the hypertrophic response and DADs related arrhythmias. Indeed, recent studies have provided evidence that inhibition of reversed mode by KB-R7943 is effective in reducing cytosolic Ca$^{2+}$ overload, cell injury and arrhythmias in different kinds of preparation and experimental conditions. [107, 108]. Few data are available regarding HF. In failing myocytes it has been shown that inhibition of NCX improves excitation-contraction coupling in HF [109]. So, therapeutic intervention, which inhibits reversed mode or activates forward mode NCX might reduce Ca$^{2+}$ overload in HF and as a consequence reduce the hypertrophic response and DADs related arrhythmias. In addition, the regulatory mechanisms of the NCX protein, which are achieved by a variety of extracellular and intracellular factors, are in principle therapeutic targets to influence the activity of NCX.

**THE Na$^+$/K$^+$-ATPase**

The Na$^+$/K$^+$-ATPase (Na/K-pump) is found at the plasma membrane and provides the major route for cellular Na$^+$ efflux [110, 111]. The energy derived from the hydrolysis of ATP is used by the Na/K-pump to extrude three Na$^+$ ions for two K$^+$ ions. A principal modulator of Na/K-pump activity is $[\text{Na}^+]_i$, [112-114]. In this way the Na/K-pump keeps $[\text{Na}^+]_i$ low and $[\text{K}^+]_i$ high, thereby maintaining the asymmetric gradients of these ions across the sarcolemma.

The myocardium expresses three Na/K-pump $\alpha$-subunit isoforms ($\alpha_1$, $\alpha_2$, and $\alpha_3$) and one $\beta_1$-subunit isoform. The $\alpha$-subunits differ in affinity for intracellular Na$^+$ and for the inhibitor ouabain. In addition, also a Na/K-pump regulatory $\gamma$-subunit, phospholemman (PLM), is expressed in the heart.

Modulation of the Na/K-pump activity can be achieved by changing expression levels, shifting the $\alpha$-isoform expression, and changing PLM phosphorylation. PLM phosphorylation by protein kinase A (PKA) and protein kinase C (PKC), causes dissociation of PLM from the $\alpha$-subunits thereby increasing the Na$^+$ and K$^+$ affinity of the Na/K-pump [115]. Further, it should be realized that the sodium gradient across the sarcolemma largely depends on the energy that can be transferred to the Na/K-pump by hydrolysis of ATP $\Delta G_{\text{ATP}}$ [116]. A rather small change of $\pm 2$ kJ/mole of $\Delta G_{\text{ATP}}$ will shift the thermodynamic equilibrium of the Na/K-pump and consequently, a 1.5 mM higher $[\text{Na}^+]_i$. In rabbit failing myocytes it has been shown that $\Delta G_{\text{ATP}}$ was $\pm 2$ kJ/mole lower compared to control myocytes [25].

Several studies have reported a decrease in the activity of the Na/K-pump in hypertrophy and HF due to downregulation of the number of pumps and/or due to shift in isoform expression [117-125]. However, most studies regarding expression of the Na/K-pump were performed in tissue homogenates and could reflect changes in non-myocytes [126]. In addition, these experiments cannot dis-criminate between sarcolemma and intercellular Na/K-pump expression. It is therefore hard to show a clear relationship between the expression and activity of Na/K-pump. In this respect it is surprising that there are only a few reports in which Na/K-pump function activity is actually measured in the setting of HF. In myocytes from rats with HF, the maximal Na$^+$ efflux rate was reduced with unchanged $[\text{Na}^+]_i$. In contrast, in myocytes from dogs with hypertrophy induced by chronic atrioventricular block, maximal Na/K-pump activity is unchanged but $[\text{Na}^+]_i$-affinity was reduced [28]. In myocytes from rabbits, with volume and pressure overload induced HF, neither maximal Na$^+$ efflux rate nor the affinity of Na/K-pump was reduced [23]. So, it seems that Na/K-pump expression may be altered in cardiac myocytes without a change in maximal activity. Moreover, from steady-state considerations it follows that the Na/K-pump in HF, even if down-regulated at the protein level, is capable to balance increased sodium influx. Thus, the actual activity of Na/K-pump must be higher in HF. Increased $[\text{Na}^+]_i$ in HF could kinetically compensate for down-regulation of the Na/K-pump and increased sodium influx in order to achieve steady-state. Another reason for the discrepancy between the expressions and activity of the Na/K-pump might be altered regulation of the pump in HF. However, signalling cascades involved in hormonal regulation, in particular, are varied and complex. Alterations in regulation may be the result of posttranslational modification such as phosphorylation. It remains to be determined whether and to what extent such modifications affect the Na/K-pump, per se, or some regulatory component [128, 129].

Following the argumentation that prevention of an increased $[\text{Na}^+]_i$ and the subsequent $[\text{Ca}^{2+}]_i$ rise may prove beneficial in the patients at risk to develop hypertrophy and HF. Activation of the regulation mechanisms and/or direct activation of the Na/K-pump might be therapeutically beneficial in reducing $[\text{Na}^+]_i$, and $[\text{Ca}^{2+}]_i$, development of hypertrophy and HF and prevent the remodelling. Whether Na/K-pump activation will be an effective treatment for hypertrophy and HF remains to be investigated and needs development of new drugs. Until now inhibition of the Na/K-pump (digoxin) is used to increase contractility of the heart in the setting of HF. Inhibition of the pump results in a further increase of $[\text{Na}^+]_i$, and secondarily to an increase of $[\text{Ca}^{2+}]_i$ and contractility. Although, the short term effect of Na/K-pump inhibition is beneficial in the treatment of HF because of increased contractility. The long term effect might be detrimental because of the increase of $[\text{Na}^+]_i$, and $[\text{Ca}^{2+}]_i$. In this respect it has been shown that reduction of Na$^+$ efflux associated with Na$^+/K^+$-pump inhibition promotes cardiac hypertrophy [130, 131].

**SUMMARY**

The sodium ion transport pathways that regulate $[\text{Na}^+]_i$ maintain normal Ca$^{2+}$ handling, contractility and electrical activity of healthy cardiomyocytes. Under pathophysiological conditions, such as hypertrophy and HF, $[\text{Na}^+]_i$ is increased due to an unbalanced increased Na$^+$ influx. The increased Na$^+$ influx in HF may originate from increased NHE-1, NBC and NKCC activity, and altered inactivation of the Na$^+$-channels. Increased $[\text{Na}^+]_i$ in HF causes NCX mediated elevation of $[\text{Ca}^{2+}]_i$, which is known to be a hypertrophic signal. Cardiac hypertrophy is a major risk factor for cardiac death and commonly precedes the development of HF. The altered Na$^+$ and Ca$^{2+}$ handling in HF leads to electrical remodelling.
increased incidence of EADs and DADs, which are known
triggers for arrhythmias. In this respect, it has been shown experi-
mentally that normalizing Na⁺ and/or Ca²⁺ handling is beneficial in
the prevention and regression of hypertrophy and HF and related
arrhythmias. These findings may help to find new therapeutic
strategies for the treatment of cardiac hypertrophy and HF.

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