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Na^+ transport in the normal and failing heart – remember the balance

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Abstract

In the heart, intracellular Na^+ concentration ($[Na^+]_i$) is a key modulator of Ca^{2+} cycling, contractility and cardiac myocyte metabolism. Several Na^+ transporters are electrogenic, thus they both contribute to shaping the cardiac action potential and at the same time are affected by it. $[Na^+]_i$ is controlled by the balance between Na^+ influx through various pathways, including the Na^+/Ca^{2+} exchanger and Na^+ channels, and Na^+ extrusion via the Na^+/K^+-ATPase. $[Na^+]_i$ is elevated in HF due to a combination of increased entry through Na^+ channels and/or Na^+/H^+ exchanger and reduced activity of the Na^+/K^+-ATPase. Here we review the major Na^+ transport pathways in cardiac myocytes and how they participate in regulating $[Na^+]_i$ in normal and failing hearts.

Keywords

intracellular Na^+ concentration; myocyte; Na^+/K^+-ATPase; Na^+/Ca^{2+} exchanger; Na^+/H^+ exchanger; heart failure

1. Na^+ transport and heart function

1.1. $[Na^+]_i$ and cardiac contractility

Intracellular Na^+ concentration ($[Na^+]_i$) is an important modulator of cardiac myocyte Ca^{2+} cycling and contractility [1]. This regulation is mediated mainly by the Na^+/Ca^{2+} exchanger (NCX), which transports three Na^+ ions in exchange for one Ca^{2+} ion, and is the main route for Ca^{2+} extrusion from cardiac myocytes [2]. During the cardiac cycle, NCX needs to extrude exactly the same amount of Ca^{2+} that enters through L-type Ca^{2+} channels (about 8 μmol/L cytosol, [2]) for the myocyte to be in steady-state. Indeed, Bridge et al. [3] have shown that the total charge carried by the nifedipine-sensitive Ca^{2+} current is twice the total charge carried by the inward NCX current, which means (assuming a $3Na^+$:$1Ca^{2+}$ stoichiometry for NCX, [4]) that all Ca^{2+} entering through Ca^{2+} channels is extruded by NCX. Thus, small changes in NCX activity may significantly alter Ca^{2+} homeostasis. NCX is unique among Na^+ transporters in that it can work in both Ca^{2+} extrusion (or forward) and Ca^{2+} influx (or reverse) mode under physiological conditions, depending on the membrane

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potential and intracellular and extracellular concentrations of Ca^{2+} and Na^+. High intracellular Ca^{2+} favors Ca^{2+} extrusion whereas high $[Na^+]_i$ and membrane depolarization favor Ca^{2+} influx. NCX activity is critically regulated by $[Na^+]_i$. Even a modest (a few mM) increase in $[Na^+]_i$ causes the exchanger to extrude less Ca^{2+}, which raises the cellular and sarcoplasmic reticulum (SR) Ca^{2+} content (Fig. 1). This leads to larger Ca^{2+} transients and thus larger contractions. At the same time, higher SR Ca^{2+} load may also lead to spontaneous Ca^{2+} waves. Part of the Ca^{2+} released during a wave is extruded through NCX and the depolarizing current that is produced can generate delayed afterdepolarizations (DADs) and triggered arrhythmias. This is the basic mechanism responsible for both the inotropy and arrhythmogenesis produced by cardiac glycosides, specific inhibitors of the Na^+/K^+-ATPase (NKA) that have been used in the treatment of congestive heart failure for more than two centuries.

DADs occurring in a single myocyte (the source of depolarization) cannot trigger a premature beat in the intact heart because the strong electrotonic coupling between the myocytes acts as a sink for local depolarizing current. Mathematical models have shown that to overcome the source - sink mismatch, DADs have to occur simultaneously in a large number of cells (several hundred thousands) [5]. The requirement for the occurrence of spontaneous Ca release over a broad aggregate of myocardial cells before initiation of an extopic beat was confirmed by optical mapping in ventricular wedge preparations [6]. Such temporal synchronization of spontaneous Ca waves could be attained by localized β-adrenergic stimulation [7]. Reduced gap junction conductance, enhanced NCX, reduced inward rectifier K^+ current, fibrosis, and reduced repolarization reserve, factors that are associated with electrical remodeling in heart failure, favor the occurrence of DADs-induced ectopic beats [5,8]. Nevertheless, details about DADs triggering of premature ventricular complexes are incompletely understood.

In ischemia/reperfusion injury, NCX reversal connects an increase in $[Na^+]_i$, brought about by activation of the Na^+/H^+ exchanger (NHE) and Na^+/HCO_3^- cotransporter (NBC), an increase in slowly-inactivating Na^+ channels, Na^+ entry through connexin hemmichannels and NKA inhibition (reviewed in [9]), to Ca^{2+} overload. Not surprisingly, cardiac-specific ablation of NCX was found to confer protection against ischemia/reperfusion injury [10].

1.2. $[Na^+]_i$ and cardiac metabolism

$[Na^+]_i$ is an important regulator of cardiac metabolism. This is because $[Na^+]_i$ controls mitochondrial Ca^{2+} concentration ($[Ca^{2+}]_m$) through the mitochondrial Na^+/Ca^{2+} exchanger (Fig. 1). At high workload, for example with increasing heart rate during adrenergic stimulation, Ca^{2+} uptake into mitochondria via Ca^{2+} uniporter is elevated. High $[Ca^{2+}]_m$ stimulates several dehydrogenases involved in the tricarboxylic acid cycle [11], which leads to a faster regeneration of NADH and NADPH from NAD^+ and $NADP^+$, respectively. This limits and can even prevent decreased [NADH] during increased work driven by larger Ca^{2+} transients [12]. Faster restoration of the NADH pool allows an increased rate of electron transport and thus augments ATP production. At the same time, reduced NADPH is needed to eliminate the H_2O_2 produced by dismutation of the superoxide generated at complexes I and III of the electron transport chain [13]. In agreement with this, inhibition of mitochondrial Ca^{2+} uptake with Ru360 was found to increase the mitochondrial H_2O_2 production [14]. Thus, elevated $[Ca^{2+}]_m$ is also important in controlling the oxidative stress.

In the heart, Ca^{2+} extrusion from mitochondria occurs mostly through a Na^+/Ca^{2+} exchanger [15]. Although its existence has been accepted for a long time, the molecular identity of the mitochondrial Na^+/Ca^{2+} exchanger has remained elusive until recently, when it was shown that NCLX, the lone member of the Ca^{2+}/cation exchanger (CCX) family found in mammals [16], is in fact the long-sought mitochondrial Na^+/Ca^{2+} exchanger [17,18]. Different from

the sarcolemmal NCX, Li^+ can substitute for Na^+ in NCLX and its activity is inhibited by CGP-37157 [17]. Both features are hallmarks of mitochondrial Na^+-dependent Ca^{2+} efflux. While initially thought to be electroneutral ($2Na^+$:$1Ca^{2+}$), it seems accepted now that mitochondrial Na^+/Ca^{2+} antiporter exchanges three Na^+ ions for one Ca^{2+} ion [19–21], similar to sarcolemmal NCX. Mitochondrial Na^+/Ca^{2+} exchanger has a half-maximal activity at $[Na^+]_i$=5–10 mM, very close to physiological $[Na^+]_i$. This makes the exchanger very sensitive to changes in $[Na^+]_i$. Elevated $[Na^+]_i$ accelerates mitochondrial Ca^{2+} efflux and reduces $[Ca^{2+}]_m$ [22–23]. Notably, an electrogenic mitochondrial Na^+/Ca^{2+} exchanger will lower $[Ca^{2+}]_m$ following an increase in $[Na^+]_i$ even in the absence of a Na^+ gradient across the inner mitochondrial membrane due to the large, negative mitochondrial membrane potential.

$[Na^+]_i$ is relatively constant in the normal heart. In isolated cardiac myocytes, $[Na^+]_i$ increases significantly with increasing the pacing frequency. However, an accelerated heart rate *in vivo* is generally the result of adrenergic stimulation, which also increases Na^+ extrusion through NKA (by relieving its inhibition by the small sarcolemmal protein PLM, [24,25]). The net effect is relatively little change in $[Na^+]_i$ [26–28]. Combined with larger Ca^{2+} transients, low $[Na^+]_i$ facilitates elevated $[Ca^{2+}]_m$ and contributes to both increased ATP production to match the higher energy demand and the maintenance of redox homeostasis. $[Na^+]_i$ is however increased in pathophysiological situations such as ischemia/reperfusion and heart failure (see below). Elevated $[Na^+]_i$ led to oxidation of NAD(P)H and increased H_2O_2 formation in myocytes from failing hearts, which could be prevented by pharmacological inhibition of the mitochondrial Na^+/Ca^{2+} exchanger [29]. Higher oxidative stress may further exacerbate the increase in $[Na^+]_i$ by activating, directly or through Ca^{2+}/calmodulin-dependent kinase II (CaMKII), the slowly inactivating mode of Na^+ channels (Fig. 1) [30,31]. Thus, by controlling $[Ca^{2+}]_m$, $[Na^+]_i$ is an important parameter in matching energy supply and demand and critically regulates the production of mitochondrial reactive oxygen species in cardiac myocytes.

1.3. Na^+ transport and action potential waveform

Many Na^+ transporters are electrogenic, which means that they both contribute to shaping the action potential (AP) waveform and at the same time are affected by it. Voltage-gated Na^+ channels are responsible for the fast upstroke of the AP, however, because they inactivate within a few milliseconds, they have little effect on the AP duration. A few Na^+ channels (about 0.5%) either do not inactivate, or close and then reopen, generating a slowly inactivating, or late, Na^+ current [32,33]. Some genetic mutations in the SCN5A gene encoding cardiac Na^+ channels lead to elevated late Na^+ current [34–36], resulting in AP prolongation and long-QT syndrome type 3 (LQT3). Late Na^+ current is also increased in pathophysiological conditions such as ischemia/reperfusion [37] and heart failure [38–40], which leads to acquired LQT syndrome. AP prolongation is arrhythmogenic by facilitating the occurrence of early afterdepolarizations, particularly at slow heart rates. At the same time, elevated slowly-inactivating Na^+ current may increase $[Na^+]_i$ and cause DADs and triggered arrhythmias through the mechanism described in section 1.1 [41,42].

By extruding one net positive charge, NKA participates in membrane repolarization and thus may affect both the plateau phase of the AP and the resting membrane potential. At normal heart rates this effect is however rather small. Indeed, acute NKA inhibition depolarizes the myocytes by only 5–6 mV and slightly prolongs the AP (for a review, see [43]). Obviously, long-term NKA blockade will greatly alter Na^+ and K^+ homeostasis and depolarize the membrane. Surprisingly, a computational model of AP in human ventricular myocytes predicted that an increase of NKA, due to NKA activation by the increasingly higher $[Na^+]_i$, current is the predominant factor in AP shortening that occurs with increasing pacing rates [44]. As discussed above, $[Na^+]_i$ accumulation produced by a physiological increase in the

heart rate *in vivo* is much smaller. However, the adrenergic stimulation that accelerates the heart rate also increases the NKA current by phosphorylating PLM and thus enhancing the NKA affinity for internal $[Na^+]_i$ [24,25]. Thus, NKA may be a major contributor to AP shortening at high heart rates, particularly in humans and other species (dog, rabbit) with modest delayed rectifier K^+ current (I_{Ks}).

NCX is also electrogenic, however predicting its effect on the AP is more difficult because the NCX driving force is changing rapidly during an AP. Under physiological conditions, NCX works almost exclusively in the Ca^{2+} extrusion mode, driven by the negative membrane potential and low $[Na^+]_i$ at rest (diastole) and the high subsarcolemmal Ca^{2+} during Ca^{2+} release [2]. Thus, NCX works to depolarize the sarcolemma and increased NCX activity will prolong the AP. Schouten and Ter Keurs [45] found that reducing the forward mode of NCX by either an increase in external Ca^{2+} or a decrease in external Na^+ shortened the slow phase of repolarization in trabeculae from the rat right ventricle. When $[Na^+]_i$ is elevated, the balance of ion fluxes through NCX is shifted to reduce Ca^{2+} extrusion, and thus reduce the depolarizing inward current and shorten the AP [46]. Therefore, through changes in NKA and NCX currents, higher $[Na^+]_i$ may alleviate the AP prolongation seen in pathophysiological conditions such as heart failure [46].

2. $[Na^+]_i$ transport in and out of cardiac myocytes

Several transporters facilitate Na^+ entry into cardiac myocytes (Fig. 1), with Na^+ channels and NCX being the most important quantitatively in the normal heart. Other transporters however may become prominent in producing Na^+ overload under pathophysiological conditions. For example, the activity of NHE and NBC is increased greatly during ischemia/reperfusion due to stimulation of proton extrusion by intracellular acidosis. Under mild acidosis (pH_i=6.9), NHE and NBC may account for as much as 75% of resting Na^+ influx in cardiac myocytes [1]. Other pathways for Na^+ entry are the Na^+/Mg^{2+} exchanger, which is involved in Mg^{2+} extrusion, and $Na^+/K^+/2Cl^-$ cotransporter, which may play a role in volume regulation. $[Na^+]_i$ is maintained low by active pumping out of the cells by NKA. Here we will briefly review the structure, function and regulation of NCX, Na^+ channels and NKA. NHE and NBC are discussed in other articles in this Special Issue.

2.1. Na^+/Ca^{2+} exchanger

NCX1 (970 amino acids, ~110 kDa) is the only NCX isoform present in the heart. NCX1 was initially thought to have 11 transmembrane domains (TM) [47]. More recent topological models suggested nine TMs [48,49]. The newly-uncovered high resolution crystal structure of an NCX from Methanococcus jannaschii (NCX_Mj) identified 10 TMs [50]. Due to the similarity in sequence and hydrophobicity pattern with NCX_Mj, it is likely that NCX1 assumes a similar topology [50]. This NCX1 topology was recently confirmed by a study that re-assessed the topology of the C-terminal TMs of NCX1 [51]. Two highly conserved regions of internal repeats (α1 and α2; ~40 amino acids) are present on the N- and C-termini halves of the molecules. These α repeats are near one another in the folded protein and they contribute to the ion conduction pathways [50,52,53]. The NCX_Mj crystal structure reveals four potential cation binding sites formed exclusively by residues from the α repeats and arranged in a diamond shape [50].

The 10 TMs represent about half of the NCX1 protein. Most of the remaining half (~550 amino acids) is a large, unstructured cytoplasmic loop between TMs 5 and 6. This loop contains two separate Ca^{2+} binding domains, or β-repeats, CBD1 and CBD2. Elevated $[Ca^{2+}]_i$ allows Ca^{2+} to bind to the CBD domains, which increases the activity of the exchanger (allosteric $[Ca^{2+}]_i$-dependent activation) [54–56]. Allosteric Ca^{2+} activation occurs at physiological $[Ca^{2+}]_i$ ($K_{0.5}$=22–600 nM) and develops rapidly (within ~100 ms).

However, NCX remains active for tens of seconds after $[Ca^{2+}]_i$ returns to low levels [57–59]. Thus, NCX is substantially activated in a beating heart, with little beat-to-beat variation. While high $[Ca^{2+}]_i$ activates NCX, high $[Na^+]_i$ inhibits it (Na^+-dependent inactivation) in a time and $[Na^+]_i$-dependent manner. Na^+-dependent inactivation is probably not very important in cardiac myocytes because it occurs at $[Na^+]_i$ (>30 mM) substantially above the physiological level. $[Na^+]_i$-dependent inactivation is eliminated by an increase in membrane PIP_2. Moreover, when PIP_2 levels are high, elevated $[Na^+]_i$ induces a mode of exchange activity that does not require allosteric Ca^{2+} activation [60]. PIP_2 may also modulate NCX by affecting its membrane trafficking [61].

In cardiac myocytes, NCX is located mostly at the T-tubules [62–64]. It is however unclear whether/to what extent NCX is present at the junctions between sarcolemma and SR membrane where most of Ca^{2+}-induced Ca^{2+} release occurs. Some immunofluorescence studies indicate that NCX is not present at the junctions [65,66]. However, a more recent study using high-resolution imaging of transverse myocyte sections found that NCX partially (~27%) co-localizes with ryanodine receptors (RyRs) [67]. This study suggests that NCX is neither excluded from nor concentrated at the junctions. The mean distance between NCX and the nearest RyRs cluster was slightly smaller than would be expected from a uniform NCX distribution. NCX senses an early rise in local $[Ca^{2+}]_i$ (*vs.* bulk $[Ca^{2+}]_i$) during SR Ca^{2+} release [68,69], suggesting that NCX has some access to Ca^{2+} in the junctional cleft, in agreement with the results of Jayasinghe et al. [67]. Indeed, Ca^{2+} entry via reverse-mode NCX can trigger Ca^{2+} release from the SR at least under certain conditions [70–73], although with low efficiency. Moreover, data from NCX-KO mice [74] and from experiments where Na^+ current is manipulated [75] indicate that by priming the junctional cleft with Ca^{2+}, NCX contributes to the normal triggering of Ca^{2+} release. Of course, this effect is only likely to be relevant during the latency period before an L-type Ca^{2+} channel opens at a given junction because the local flux is ~1000 times higher for Ca^{2+} current *vs.* NCX. Immediately following SR Ca^{2+} release, Ca^{2+} extrusion through the fraction of junctionally-located NCX may limit the global cytosolic Ca^{2+} transient.

2.2. Voltage-gated Na^+ channels

Voltage-gated Na^+ channels, composed of one pore-forming α subunit and one or two auxiliary β subunits [76], mediate the rapid upstroke of the AP in cardiac myocytes. The α subunit (~240 kDa) consists of four repeat domains (I–IV), each containing six transmembrane segments (S1–S6) and one membrane reentrant domain, connected by internal and external polypeptides loops [77]. Positively charged residues in the S4 segments serve as voltage sensors. Upon depolarization, these charges move outward, triggering activation of the channel [78]. Most Na^+ channels switch off Na^+ conductance within a few milliseconds upon depolarization (channel inactivation), a process mediated by a hydrophobic isoleucine-phenylalanine-methionine motif located on the short intracellular loop connecting domains III and IV [79]. The tetrodotoxin resistant isoform $Na_v1.5$, encoded by the SCN5A gene, is the predominant α subunit in the heart. Some types of neuronal and skeletal muscle Na^+ channels have also been found in the heart (for a review, see [80]). The contribution of such channels to the total myocyte Na^+ current is small (<15%) and their physiological role is not fully elucidated. Increasing evidence suggests that these TTX-sensitive Na^+ channel isoforms may represent an intrinsic depolarization reserve and play a role in coupling electrical excitation to contraction [75, 81, 82]. However, this is still controversial as, for example, another study found no role for the neuronal Na^+ channels in SR Ca^{2+} release [83]. The auxiliary β subunits (~30–35 kDa, β1–β4 subunits) modulate channel gating, interact with extracellular matrix and play a role as cell adhesion molecules [84].

$Na_v1.5$ Na^+ channels are located both in the T-tubules and external sarcolemma [65,85], with a roughly equal distribution [86]. However, some immunofluorescence studies show $Na_v1.5$ mostly at the intercalated disks [85]. $Na_v1.5$ channels interact in complexes with a large number of regulatory proteins (for a review, see [87]). Interaction with ankyrin-G, an anchoring protein that links membrane proteins to the cytoskeleton, is essential for the proper membrane targeting of Na^+ channels. Reduced ankyrin-G expression decreases total cellular $Na_v1.5$ expression and its efficient membrane localization, as well as Na^+ current [88]. Moreover, a mutation in the ankyrin-binding motif of $Na_v1.5$ that abolishes the binding of ankyrin-G has been shown to induce Brugada syndrome, a condition associated with loss of function of Na^+ channels [89]. A recent study suggested that ankyrin-G is an essential functional component of the intercalated discs that connects the voltage-gated Na^+ channels, connexin 43, and the cardiac desmosome [90].

While most of cardiac myocyte Na^+ channels inactivate quickly, some channels (~0.5%) either do not close, or close and then reopen, generating a slowly-inactivating, late Na^+ current [32,33]. Recent evidence suggests that neuronal Na^+ channels may also be implicated in the late Na^+ current in cardiac myocytes [91]. In normal conditions, this slowly-inactivating Na^+ current is too small to significantly affect AP duration and total Na^+ influx. However, genetic mutations in the SCN5A gene or pathophysiological conditions such as ischemia [92] and heart failure [33,39] result in elevated late Na^+ current, which leads to inherited LQT3 or, respectively, acquired LQT syndrome. In heart failure, late Na^+ current may be enhanced by CaMKII-dependent phosphorylation of $Na_v1.5$ channels since CaMKII expression and activity is augmented [93,94] and overexpression of CaMKII increases late Na^+ current [95].

2.3. Na^+/K^+-ATPase

The NKA extrudes three Na^+ ions in exchange for two K^+ ions using the energy derived from the hydrolysis of one ATP molecule, and thus moves out one net charge per cycle. Internal Na^+ and external K^+ activate NKA with a half-maximal activation in the range of 10–22 mM and 1–2 mM, respectively (for a review, see [43]). Thus, NKA is ~70% saturated with respect to external K^+ at a normal concentration of 4 mM. The ATP concentration for half-maximal NKA activation is 80–150 μM [96,97], therefore under control conditions ATP is not rate limiting for the pump (normal ATP level in myocytes is 5–10 mM).

NKA is composed of three subunits: the catalytic α subunit, the auxiliary β subunit and the tissue-specific regulatory protein FXYD. The NKA-α subunit (~110 kDa) contains the binding sites for Na^+, K^+, ATP and cardiac glycosides, specific inhibitors of the enzyme. The main function of the smaller β subunit (~50 kDa) is that of a molecular chaperone. Association with β-subunit facilitates the routing to and insertion into the membrane of the α-subunit [98]. The β-subunit also modulates the ATPase activity of NKA. FXYDs are a family of proteins that associate with and modulate NKA in various tissues [99]. The small (72 amino acids) sarcolemmal protein phospholemman (PLM) is the only FXYD protein that is highly expressed in the heart and is an important NKA regulator. Unphosphorylated PLM inhibits NKA, mostly by reducing its affinity for internal Na^+ [24,25,100,101] and PLM phosphorylation by PKA or PKC relieves this inhibition [24,101]. This is similar to the way phospholamban modulates SERCA, a P-type ATPase closely related to NKA. PLM phosphorylation and the ensuing NKA disinhibition are an integral part of the sympathetic *fight-or-flight* response, by enhancing Na^+ extrusion to better keep up with the increased Na^+ influx at higher heart rates and with larger Ca^{2+} transients (which drive greater inward NCX current) [26]. This limits the rise in $[Na^+]_i$ during β-adrenergic stimulation. Thus, NKA regulation by PLM may prevent Ca^{2+} overload and triggered arrhythmias during sympathetic stimulation of the heart.

The crystal structures of NKA from pig kidney [102] and shark rectal gland [103] have been recently uncovered. The α-subunit has 10 TMs and, like SERCA, three characteristic cytoplasmic domains: the actuator, nucleotide-binding and phosphorylation domains. Two binding sites, common for K^+ and Na^+ binding, are located ~4Å apart between TMs 4, 5 and 6 [102]. A third Na^+ binding site is created by residues from TMs 5, 6 and 9. The TM helix of β-subunit runs nearly parallel to the M7 helix of the α-subunit and comes within interaction distance of NKA-α TM7 and TM10 in multiple places [103]. On the extracellular side, β-subunit makes complex interactions with the loop between TM7 and TM8 of the α-subunit. FXYD proteins (γ-subunit for the pig NKA and FXYD10 for the shark rectal gland NKA) consist of a single TM domain that is in close proximity of NKA-α TM9, on the outside of a groove formed by TM2, TM6, and TM9 [102,103]. The crystal structures identified a number of possible interaction sites between FXYD and NKA-α TM9. In a recent study we demonstrated that interaction between NKA-α-E960 and PLM-F28 sites is critical for the functional effects of PLM on NKA [104]. The conserved FXYD motif is located in the extracellular domain, just prior to the TM domain and seems to interact with both α- and β-subunits. This suggests that the FXYD region may be important for stabilizing α-β-FXYD interaction.

Three α (α1–α3) and three β (β1–β3) NKA subunit isoforms are present in the heart. NKA-α1 is the dominant, ubiquitous isoform, with NKA-α2 and NKA-α3 present in smaller amounts and only in select species. All three isoforms are present in human hearts [105], with NKA-α1 mRNA level slightly higher than that for NKA-α2 and NKA-α3 [106,107]. Fetal and neonatal rodent hearts express NKA-α1 and NKA-α3, and NKA-α3 is replaced by NKA-α2 early in development [108]. Interestingly, the reverse switch occurs in hyperthrophied or failing hearts [109,110]. The enzymatic activity and Na^+, K^+ and ATP affinities of various NKA-α isoforms are comparable (for a detailed discussion, see [111]). However, different NKA isoforms may function differently, depending on specific membrane localization. It was proposed that NKA-α2 and NKA-α3 are located mainly in the T-tubules, at the junctions with the SR, where they could regulate local NCX and $[Ca^{2+}]_i$, whereas NKA-α1 is central to determining global $[Na^+]_i$ [112]. This is still incompletely proven in cardiac myocytes as the exact localization of NKA isoforms with respect to the junctions is difficult to assess with the current techniques, and the functional evidence is mostly indirect [113–115]. The functional density of NKA-α2 isoform is ~4-times higher in the T-tubules (*vs.* external sarcolemma) in myocytes from both rats [113,116] and mice [117], whereas NKA-α1 is more uniformly distributed. Using mice in which NKA-α1 is ouabain-sensitive and NKA-α2 is ouabain-resistant we have recently showed that NKA-α2 inhibition produced a bigger increase in Ca^{2+} transient amplitude and fractional SR Ca^{2+} release than blockade of a similar number of NKA-α1 pumps [118]. Thus, NKA-α2 may have a more prominent role (vs. NKA-α1) in modulating Ca^{2+} release in cardiac myocyte.

The membrane targeting of both NKA and NCX require direct interactions with ankyrin-B, a multivalent “adaptor” protein that targets and tethers select membrane proteins to the cytoskeleton [119]. Loss-of-function mutations in the gene encoding ankyrin-B lead to complex cardiac phenotypes in humans. These phenotypes may include bradycardia, atrial fibrillation, conduction defects, stress- or exercise-induced ventricular arrhythmias and sudden cardiac death (for a review, see [120]). Decreased ankyrin-B function resulted in reduced NKA and NCX targeting to the T-Tubules as well as reduced overall NKA and NCX protein level in cardiac myocytes [121]. Notably, the clinical severity of human ankyrin-B loss-of-function variants has been directly linked with the inability to target NCX and NKA to the cardiac myocyte sarcolemma [122]. Cardiac myocytes from mice heterozygous for a null mutation in ankyrin-B show larger Ca^{2+} transients and SR Ca^{2+} content [121]. We have recently found larger Ca^{2+} spark frequency but unchanged total

RyR-mediated SR Ca^{2+} leak in ventricular myocytes from ankyrin-B heterozygous *vs.* wild-type mice [123]. Such a bias toward more coordinated RyRs gating is likely due to different RyR regulation at the cytoplasmic side and results in an increased propensity for Ca^{2+} waves, which may contribute to the increased arrhythmogenicity caused by ankyrin-B loss-of-function.

3. $[Na^+]_i$ balance in the normal heart

Resting $[Na^+]_i$ is ~4–8 mM in ventricular myocytes from rabbit, guinea-pig and dog [124–130] and somewhat higher (9–14 mM) for rat and mouse [24,127–129,131,132]. While accurate measurements are lacking, resting $[Na^+]_i$ in human myocytes is believed to be in the 4–10 mM range. There might be sub-regional differences in $[Na^+]_i$ in the ventricle [130,133]. Higher $[Na^+]_i$ was found in epicardial *vs.* endocardial myocytes in rabbit left ventricle [133], while the opposite was observed in canine ventricle [130]. In rabbit, the NKA expression and current density were similar in the two regions [134], whereas NKA current was significantly larger in epicardial *vs.* endocardial canine myocytes [130]. Clearly, more data are needed regarding a possible transmural gradient in $[Na^+]_i$ (and NKA current) and its functional consequences, as well as on $[Na^+]_i$ regulation in the atria.

The total Na^+ influx in resting myocytes is ~1 mM/min [1]. For myocytes to be at steady-state, this Na^+ influx has to be matched by Na^+ efflux through NKA. Fig. 2A shows the relative contribution of various Na^+ entry pathways to this resting Na^+ influx, showing rather little variation between different routes. The estimates are based in part on our measurements in rabbit ventricular myocytes [127] and some extrapolations from guinea-pig data [135,136].

In isolated myocytes, $[Na^+]_i$ increases during stimulation in a frequency dependent manner. This is mainly because Na^+ influx per unit time is higher due to more frequent activation of NCX and Na^+ channels. During electrical stimulation, NCX is likely the dominant route for Na^+ entry, bringing in almost three times more Na^+ than Na^+ channels or other pathways combined (Fig. 2B). While at rest ion fluxes through NCX are relatively small (mainly due to low diastolic $[Ca^{2+}]_i$), during electrical stimulation NCX has to remove ~8 μM Ca^{2+} that enters via Ca^{2+} current during each AP. For a myocyte contracting at 1 Hz, this means that NCX brings in ~1.5 mM/min Na^+, about 5–6 fold more than in a resting cell. Na^+ channels also bring in considerably more Na^+ during electrical pacing than at rest. The activation and availability curves of Na^+ channels overlap such that there is almost no steady-state availability at potentials where activation is appreciable. We have measured a tetrodotoxin-sensitive resting Na^+ influx of 0.18 mM/min in rabbit ventricular myocytes [137], which would require a window Na^+ current ~0.01% of the peak current [1]. During the AP upstroke, Na^+ current is very large, but very brief, resulting in an additional Na^+ influx of ~8 μM associated with each AP [1]. For a cell contracting at 1 Hz, this means that Na^+ channel activation contributes about 0.5 mM/min to the rate of Na^+ influx. Thus, Na^+ influx in contracting myocytes is about 3 mM/min, surprisingly only three times larger than at rest. A new steady-state $[Na^+]_i$ is reached when this higher Na^+ influx is matched by an elevated NKA-mediated Na^+ extrusion. During pacing, NKA is activated mainly by the increased $[Na^+]_i$ but could also be stimulated via a nitric oxide and phospholemman-dependent mechanism [138].

4. $[Na^+]_i$ balance in the failing heart

$[Na^+]_i$ is elevated in heart failure (HF), both in humans and in animal models [137,139–142]. By favoring more Ca^{2+} influx via NCX, elevated $[Na^+]_i$ may limit the contractile dysfunction in HF. Longer AP and smaller Ca^{2+} transients also favor Ca^{2+} influx via NCX in HF, but the effect seems to be less important quantitatively than that produced by higher

$[Na^+]_i$ [137]. However, high $[Na^+]_i$ may also negatively affect the cardiac metabolism and oxidative state.

Both larger Na^+ influx and reduced Na^+ extrusion may contribute to elevate $[Na^+]_i$ in HF. Protein expression of α_1-, α_3- and β_1-subunits of NKA are reduced in failing human myocardium [143], with no changes in the mRNA levels [144]. Protein and mRNA levels of the dominant NKA-α_1 isoform are unchanged in most rat HF models, whereas NKA-α_2 is generally reduced and NKA-α_3 is increased [145]. All three NKA α-subunit isoforms showed lower protein expression in myocytes from rabbits with pressure and volume overload-induced HF [146]. It is difficult however to directly correlate such biochemical findings to NKA function in myocytes, as protein expression measurements cannot differentiate between internalized *vs.* sarcolemmal NKA nor between functional and inactive pumps. Moreover, NKA may be regulated differently in HF. Indeed, we found reduced NKA expression (by ~36%, [146]) but unchanged function (both maximal Na^+ transport rate and apparent affinity for internal Na^+) [137] in myocytes from failing rabbit hearts. This apparent paradox is likely caused by reduced PLM protein expression and increased phosphorylation of PLM, which disinhibits NKA [146]. In this context, it is surprising that very few studies address NKA function in HF. Myocytes from rats with HF following myocardial infarction showed a reduction in the maximal Na^+ extrusion rate (mainly through NKA-α2 isoform) but unchanged $[Na^+]_i$-affinity [110,147]. In contrast, myocytes from dogs with chronic atrioventricular block and hypertrophy have unaltered maximal NKA pump current and reduced $[Na^+]_i$-affinity [148]. Smaller maximal NKA current, caused mainly by a reduction in the current carried by the α2 isoform seems to underlie the $[Na^+]_i$ increase in mice with end-stage HF following SERCA2 knockout [141].

Larger Na^+ influx could also cause elevated $[Na^+]_i$ in HF. We [137] and others [140] found this to be the case for myocytes from rabbits with pressure and volume-overload induced HF. We found that the initial slope of $[Na^+]_i$ rise upon NKA inhibition was twice as large as in myocytes from normal hearts [137]. Most of this elevated Na^+ entry was TTX-sensitive, suggesting a role for Na^+ channels. As discussed in section 2.2, late Na^+ current is increased in HF and this may contribute to the increased Na^+ influx. Indeed, ranolazine, a late Na^+ current inhibitor, was found to reduce $[Na^+]_i$ and diastolic Ca^{2+} overload in failing human hearts [40]. NHE upregulation may also participate in elevated Na^+ influx in HF [140]. Moreover, chronic treatment with cariporide, an NHE inhibitor, prevented the onset of HF in rabbits with pressure and volume overload [149]. One of the difficulties in assessing the contribution of different pathways to Na influx in HF lies in the uncomplete specificity of the pharmacological inhibitors. For example, cariporide also partially inhibits late Na^+ channels [150] at concentrations used to block NHE.

5. Conclusions

In summary, $[Na^+]_i$ and Na^+ transport are key factors for regulation of Ca^{2+} cycling, contractility, action potential waveform and metabolism in cardiac myocytes. $[Na^+]_i$ is the result of a delicate balance between Na^+ influx and efflux. Perturbation of this balance in HF results in elevated $[Na^+]_i$, with important consequences on cardiac myocyte function. While we have learned a great deal about Na^+ regulation in the heart, more data are needed regarding Na^+ regulation in the human heart, regional differences in $[Na^+]_i$ and Na^+ transport (ventricle *vs.* atria, endocardial *vs.* epicardial) and the mechanisms responsible for $[Na^+]_i$ dysregulation in HF.

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Abbreviations list

AP	action potential
$[Ca^{2+}]_i$	concentration of free Ca^{2+} in the cytosol
$[Ca^{2+}]_m$	concentration of free Ca^{2+} in the mitochondrial matrix
CaMKII	Ca^{2+}/calmodulin dependent kinase II
DAD	delayed afterdepolarization
FXYD	family of proteins that are specific Na/K-ATPase regulators
$[Na^+]_i$	intracellular Na^+ concentration
NBC	Na^+/HCO_3^- cotransporter
NCX	Na^+/Ca^{2+} exchanger
NHE	Na^+/H^+ exchanger
NKA	Na^+/K^+-ATPase
PLM	phospholemman
RyR	ryanodine receptor
SR	sarcoplasmic reticulum
TM	transmembrane domain

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Highlights

- We review the major Na transport pathways in cardiac myocytes
- $[Na]_i$ modulates myocyte Ca cycling, contractility, action potential and metabolism
- We discuss the balance of Na fluxes in normal hearts and in heart failure
- $[Na]_i$ is elevated in heart failure

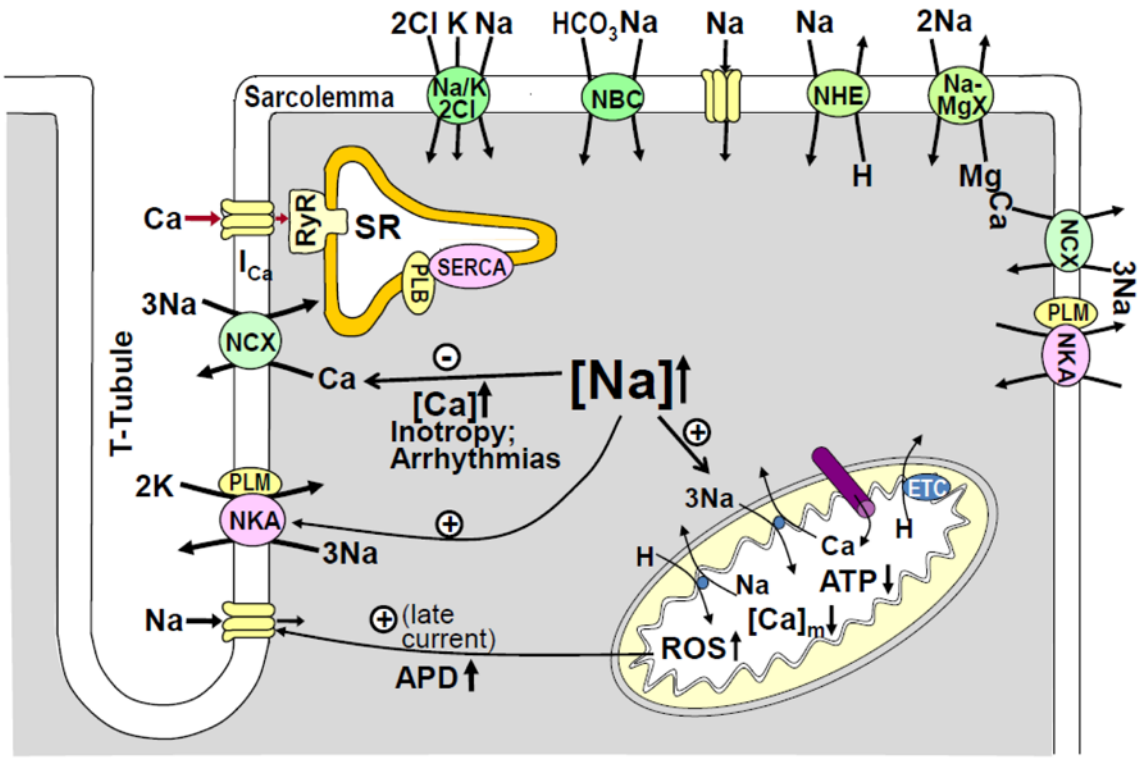

Figure 1. $[Na^+]_i$ regulation and Na^+ transport in cardiac myocytes

Cartoon showing the main Na^+ transporters in cardiac myocytes and the mechanisms by which an increase in $[Na^+]_i$ affects $[Ca^{2+}]_i$ and contractility, AP duration and cardiac metabolism.

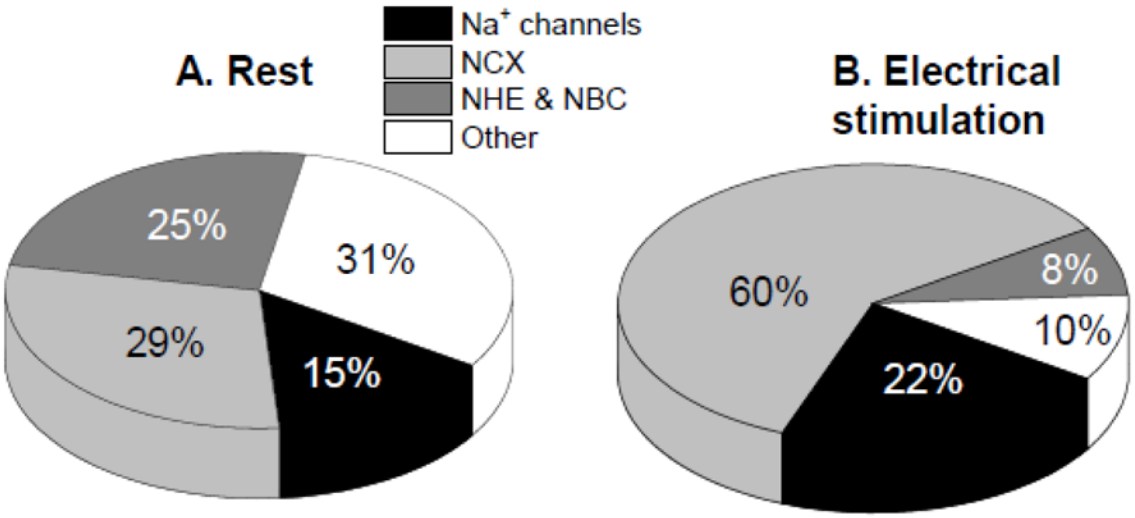

Figure 2. The relative contribution of different Na^+ entry pathways to Na^+ influx

in (A) resting myocytes and (B) myocytes contracting at 1 Hz. The estimates are based in part on our measurements in rabbit ventricular myocytes [124] and some extrapolations from guinea-pig data [132,133] and correspond to mammalian species with lower resting $[Na^+]_i$ (i.e. other than rat and mouse).