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REVIEW

Na^+/H^+ exchanger and cardiac hypertrophy☆

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Abstract Reactive cardiac hypertrophy (CH) is an increase in heart mass in response to hemodynamic overload. Exercise-induced CH emerges as an adaptive response with improved cardiac function, in contrast to pathological CH that represents a risk factor for cardiovascular health.

The Na^+/H^+ exchanger (NHE-1) is a membrane transporter that not only regulates intracellular pH but also intracellular Na^+ concentration. In the scenario of cardiovascular diseases, myocardial NHE-1 is activated by a variety of stimuli, such as neurohumoral factors and mechanical stress, leading to intracellular Na^+ overload and activation of prohypertrophic cascades. NHE-1 hyperactivity is intimately linked to heart diseases, including ischemia-reperfusion injury, maladaptive CH and heart failure.

In this review, we will present evidence to support that the NHE-1 hyperactivity constitutes a ''switch on/off'' for the pathological phenotype during CH development. We will also discuss some classical and novel strategies to avoid NHE-1 hyperactivity, and that are therefore worthwhile to improve cardiovascular health.

PALABRAS CLAVE
Hipertrofia;
Intercambiador sodio/hidrógeno;
IGF-1, ejercicio;
Estiramiento

Intercambiador Na^+/H^+ e hipertrofia cardiaca

Resumen La hipertrofia cardiaca (HC) reactiva es un incremento de la masa cardiaca, como respuesta a la sobrecarga hemodinámica. La HC inducida por ejercicio surge de una respuesta adaptativa con mejora de la función cardiaca, en contraste a la HC patológica, que representa un factor de riesgo para la salud cardiovascular.

El intercambiador Na^+/H^+ (NHE-1) es un transportador de la membrana que no solo regula el pH intracelular, sino también la concentración de Na^+ intracelular. En el escenario de las enfermedades cardiovasculares, el NHE-1 miocárdico se activa por una serie de estímulos, tales como los factores neurohumorales y el estrés mecánico, que origina una sobrecarga intracelular

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de Na^+ y la activación de cascadas pro-hipertróficas. La hiperactividad de NHE-1 está íntimamente ligada a las enfermedades cardiacas, incluyendo lesión por isquemia-reperfusión, HC mal adaptada e insuficiencia cardiaca.

En esta revisión, presentaremos la evidencia que respalda que la hiperactividad de NHE-1 constituye una «conexión/desconexión» para el fenotipo patológico durante el desarrollo de la HC. También trataremos algunas estrategias clásicas y nuevas para evitar la hiperactividad de NHE-1 y, por tanto, mejorar considerablemente la salud cardiovascular.

Introduction

Cardiac hypertrophy (CH) is defined as an increase in cardiac mass over the normal values for the corresponding sex, age and body size. It can be the result of genetic alterations or the consequence of increased workload and neurohumoral activation, this latter being identify as reactive CH.

CH is usually characterized by an increase in cardiomyocyte size and thickening of ventricular walls. Even though at the beginning it can be interpreted as an adaptive response to maintain cardiac function, in settings of sustained stress and as time progresses, these changes are recognized as maladaptive, ultimately leading to heart failure.[1,2]

The cardiac isoform of the Na^+/H^+ exchanger (NHE-1), a constitutive membrane protein ubiquitously expressed in almost every mammalian cell type, has been widely recognized to be critically involved in CH development and evolution to heart failure under conditions of cardiovascular diseases.[3–7] Moreover, its specific inhibition resulted in prevention/regression of hypertrophy.[6,8–14] However, it seems not to be involved under physiological stimulus for CH development.

In this review, we aim to summarize the current knowledge about the key role played by the overactivity of the NHE-1 in determining the type of cardiac hypertrophy developed. We will also provide evidence about the signaling pathways underlying NHE-1 activation as well as data supporting different strategies to inhibit NHE-1 activity to prevent or induce the regression of pathologic CH development and progression.

Cardiac hypertrophy: physiological and pathological types

At the cellular level, the heart is composed of cardiac myocytes (muscle cells) and nonmyocytes (e.g. fibroblasts, endothelial cells, mast cells, vascular smooth muscle cells), surrounded by extracellular matrix.[15] Even though ventricular cardiac myocytes represents only one-third of the total cell number, they account for 70–80% of the heart's mass.[15,16] In mammals, at birth or soon after, the majority of cardiac myocytes lose the capacity to proliferate, occurring heart growth primarily via an increase in myocyte size.[17] The inability of adult cardiac myocytes to divide has recently come under some debate,[18,19] although it remains very uncertain. Interestingly, it has been demonstrated that cardiomyogenesis can be activated by exercise in the normal and injured adult mouse heart.[20]

As we already mentioned, CH is broadly defined as an increase in heart mass. In response to an increase in load (e.g. pressure overload in a setting of hypertension) and in order to maintain cardiac output and counterbalance wall stress the cardiomyocytes enlarge leading to CH development.[21,22] This reactive CH can be classified as either physiological (''adaptive'') or pathological (''detrimental''). Physiological heart growth includes normal postnatal growth, pregnancy- and regular exercise-induced CH. In contrast, pathological growth occurs in response to chronic pressure or volume overload in a disease setting (e.g. hypertension, valvular heart disease, post myocardial infarction, etc.).

Both physiological and pathological heart growth are associated with an increase in heart mass; however pathological hypertrophy is also typically associated with loss of myocytes with fibrotic replacement, re-expression of fetal isoforms of contractile proteins, cardiac dysfunction, and increased risk of heart failure and sudden death.[23] In contrast, physiological CH is associated with normal cardiac structure with proportional increase in cardiomyocytes size and collagen and normal or even improved cardiac function. Moreover, exercise- and pregnancy-induced physiological CH is reversible when the growth stimulus ceases.[24–26]

The Na^+/H^+ exchanger: structure, function and activity regulation

The NHE is an important regulator of intracellular pH (pH_i) and sodium ($[Na^+]_i$) homeostasis by virtue of its ability to extrude intracellular protons in exchange for sodium with a 1:1 stoichiometric relationship.[27] The inward gradient of Na^+, mainly maintained by the Na^+/K^+ ATPase, provides a constant driving force for H^+ extrusion and Na^+ influx through the NHE.

Nine different isoforms of the NHE have been recognized thus far; among them, the isoform 1 (NHE-1) is widely distributed and the most abundantly expressed in the heart.[28]

The NHE-1 is an 815 amino acid residue protein with a predicted molecular mass of 85 kDa with an N-terminal membrane-associated domain (~500 amino acid residues) and a long C-terminal cytoplasmic tail. The membrane

domain, composed of 12 transmembrane regions connected by intracellular and extracellular loops, is associated with the ionic transport and contains the allosteric H^+ sensor site that determines the exquisite sensitivity of the exchanger to intracellular H^+.[29] The cytoplasmic domain (~300 amino acid residues) is involved in the regulation of the exchanger activity by several mechanisms. Removal of the distal region of the cytosolic tail causes a shift of the pH_i sensitivity to the acidic side and an important inhibition of NHE-1 activation by growth factors. Recently Fliegel's group demonstrated that several residues of the intracellular loop 5 were critical for proton sensing and ion transport.[29]

In Table 1 we summarize the mechanisms known to influence NHE-1 activity, including the phosphorylation or dephosphorylation of the cytoplasmic domain, the interaction with calcium–calmodulin and the union with accessory proteins or pharmacological drugs.

Causes and consequences of cardiac hypertrophy: role of the NHE-1

Both physiological and pathological CH can be the result of multiple intracellular signaling pathways triggered by membrane receptors activated by neurohumoral factors and/or myocardial stretch. However, important differences exist between the molecular targets activated in both types of CH. In the case of physiological heart growth the IGF-1-PI3K(p110α)-AKT pathway seems to be the prevailing while in pathological hypertrophy the GPCR-Gαq plays a key role. However, rather than distinct activation of intracellular pathways, it is probably more accurate to consider the resulting morphological and functional cardiac outcome a consequence of the balance between the activation of various signaling cascades.

Myocardial stretch and pathological ch

Hemodynamic overload is translated as myocardial stretch. In this sense several experimental models have been performed to mimic cardiac overload under controlled conditions. Among then, isolated neonatal and adult rat cardiac myocytes,[23–38] multicellular preparations like papillary muscles from different species,[33,39–47] and even whole rat and pig hearts[48–51] have been stretched to induce mechanical deformation and activation of the intracellular prohypertrophic signaling pathways involved in CH.

In this sense, our group has widely demonstrated that myocardial stretch induces the release of angiotensin II (Ang II) that activates the AT1 receptor inducing the release and formation of endothelin (ET). This latter binds to the ET_A receptor and activates the NHE-1 by the ERK 1/2-p90rsk dependent phosphorylation at residue serine 703.[30–32] As a consequence, intracellular sodium ($[Na^+]i$) augments and modifies the thermodynamic conditions for the Na^+/Ca^{2+} exchanger (NCX), decreasing Ca^{2+} efflux (forward mode of operation of the NCX) and/or an increasing Ca^{2+} influx (reverse mode), finally leading to an increase in intracellular Ca^{2+} ($[Ca^{2+}]i$). The rise in $[Ca^{2+}]i$ favors the activation of prohypertrophic molecules among which the phosphatase calcineurin seems to be critically involved in pathological CH development.[33] Increased production of reactive oxygen species (ROS) as a result of Ang II/ET stimulation of NADPH oxidase may be involved in the activation of ERK 1/2-p90rsk pathway.[34,35] Moreover, ROS probably participate in several steps of the intracellular signaling pathway triggered by myocardial stretch as it is depicted in Fig. 1.[35–37]

The initial step of the stretch-induced signaling cascade, the release of Ang II, was first proposed by Sadoshima et al.[38] in isolated neonatal rat ventricular myocytes. In fact, this group of researchers found that the culture medium of the stretched myocytes (conditioned medium) induces immediate-early genes and prohypertrophic signaling pathways in non-stretched myocytes.[39] Later, van Wamel et al.,[40] demonstrated that the conditioned medium from stretched myocytes contained Ang II and ET-1. Moreover, Ito et al.[41] found, in neonatal rat cardiomyocytes, that Ang II promoted the release/formation of ET-1 and that the hypertrophic effect of Ang II was blocked by blunting ETA receptor activation, supporting that ET-1 was an autocrine/paracrine intermediate in the mechanism of Ang II-induced CH. Interestingly, Yamazaki et al.[42] not only reported that stretch increases the release of ET-1 to the culture medium, but also the activation of MAPKs and NHE-1 in neonatal rat cardiomyocytes.

The analysis of the mechanical counterpart that follows myocardial stretch, represents a useful model to visualize the participation of the local Ang-ET system in the chain of events depicted in Fig. 1. The stretch of cardiac muscle increases developed force in two phases. The first phase, which occurs rapidly, is thought to be the basis of the Frank-Starling mechanism and is induced by an increase in myofilament Ca^{2+} sensitivity. The second phase or slow force response (SFR) occurs gradually and is due to a progressive rise in the amplitude of the Ca^{2+} transient, a finding first reported by Allen and Kurihara [43] and later confirmed by several other groups of researchers.[43–45] The reverse mode of the NCX, as a consequence of NHE-1 activation and $[Na^+]i$ accumulation would be the source for the augmentation in $[Ca^{2+}]i$.[44,46–53]

In vivo studies in pig hearts showed that the first molecular response to pressure overload was the disappearance of the granular staining corresponding to Ang II stores in the cytoplasm of cardiomyocytes 30 min after the imposed overload.[54] Furthermore, in situ mRNA hybridization revealed that ventricular myocytes were the source for ET-1 in the hypertrophied hearts in vivo.[55]

Thus, there are converging pieces of evidence coming from different experimental models supporting the early activation of the local Ang-ET after myocardial stretch, leading to NHE hyperactivity.

NHE-1 hyperactivity and hypertensive cardiac hypertrophy

In 1995 an enhanced activity of the NHE-1 in the hypertrophied myocardium of the spontaneously hypertensive rats (SHR) was reported.[3,56] Interestingly, experiments in our laboratory showed that the hyperactivity of the exchanger in this experimental model was not accompanied by an increase in pHi due to a simultaneous activation of the acidifying anion exchanger (AE).[57] The hyperactivity of the NHE-1 was associated with the phosphorylation in serine 703, but

Table 1 Factors that regulate the NHE-1 activity.

Regulation mechanism	Factors that regulate the NHE-1 activity	Site of interaction	Effect on NHE-1 activity	References
Pharmacological inhibitors	Amiloride, EIPA, Benzoilguanidine, zoniporide (CP597396) and SM20550.	Binding to the Na^+-binding site	–	90,94
	Empagliflozine, canagliflozine and dapagliflozine	Possibly binding to the Na^+-binding site	–	87,88
Phosphorylation	ERK1/2	Serine 770 and Serine 771	+	95
	P90RSK	Serine 703	+	96–98
	NcK interacting kinase	Aminoacids 538–638	+	99
	CAMKII	-Serine648, Serine703 and Serine796 -Non-canonical sites.	+	100,101
	PKC	¿?	+	102,103
	PKD	probably through an indirect mechanism	–	104
	AKT	Serine 648	+ or –	105,106
	P38	?	+	107
	14–3–3 proteins	consensus sequence specific for binding of 14–3-3 proteins RXXpSXP (X refers to any amino acid, and pS represents phospho-serine residue).	+	96,108
	β-Raf	Thr653	+	109
Desphosphorylation	Protein phosphatase 1and 2 (PP1 and PP2).	Cytosolic tail		110–112
Interaction with accessory proteins	Calmodulin (CaM)	Binding sites located in neighboring regions of NHE-1 (amino acids 636–656 and 657–700). Binding site: aminoacids 715–720 (PVITID)	+, when they bind Ca^{2+} +	113,114
	CHP1 and CHP3	Arginine-516 to Histidine-540 of NHE-1	–, when they bind Ca^{2+}	115
	ATP	Depletion of ATP, decrease NHE-1 activity, probably due to the NHE-1 is constitutively phosphorylated or by a yet-to-be identified cofactor, that need ATP to interact with NHE-1.	–	116–119
	PIP_2 (inositol 4, 5 biphosphate)	Two potential PIP2-binding sites were identified. NHE1-PIP2 interaction is required for basal exchange activity, and dephosphorylation of PIP2 seems to be responsible for NHE-1 inhibition depends on ATP-depletion		119,120
	CAII (carbonic anhydrase II)	Cytosolic tail	+	121
	Actin-binding proteins of the ezrin, radixin, and moesin family	Cytosolic tail	Structural role for NHE-1 in regulating cytoskeleton (independent of its function).	122,123
	Daxx	Cytosolic tail	+	124

– or + indicate inhibition or activation of the exchanger, respectively. Benzoilguanidine include HOE642 (cariporide) and HOE694, EMD96785 (eniporide), BIIB513 and BIIB723. CHP1: Calcineurin B homologous protein and CHP3: Tescalcin.

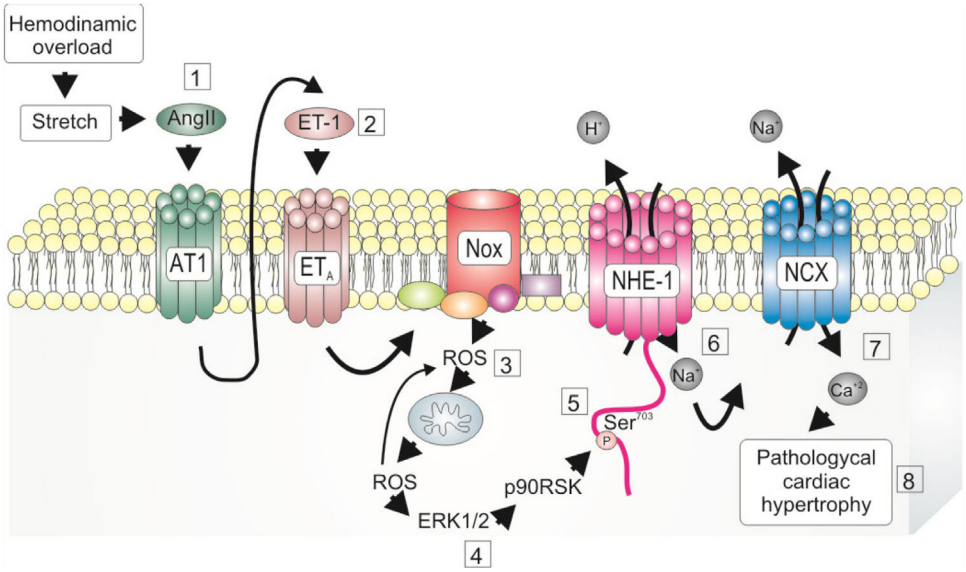

Figure 1 Role of NHE-1 hyperactivity in the development of hypertensive cardiac hypertrophy. Hemodynamic overload is translated as myocardial stretch. The main steps of the intracellular signaling pathway are: 1 – release of AngII/activation of AT1 receptor, 2 – release/formation of endothelin-1 (ET-1)/activation of ET-1 receptor, 3 – increase of reactive oxygen species (ROS) production by NADPH oxidase and mitochondria, 4 – redox-dependent p90RSK activation, 5 – NHE-1 phosphorylation/activation, 6 – NHE-1 hyperactivity and increase in intracellular Na+ concentration, and, 7 – increase in Ca2+ transient amplitude through reverse Na+/Ca2+ exchanger (NCX), 8 – activation of the calcineurin-NFAT signaling pathway responsible for triggering pathological hypertrophy.

not in serine 648, on the cytosolic tail of the exchanger, as it was reported by Yeves et al.[14] The specific inhibition of the NHE-1 induces the regression of myocardial hypertrophy in the SHR, even without normalizing blood pressure.[58,59]

Interestingly, Nakamura et al.[60] in 2008 demonstrated that cardiac overexpression of a constitutively active NHE-1 was sufficient to generate Ca^{2+} signals that induce CH and heart failure. Similar results were also obtained in neonatal rat ventricular cardiomyocytes in which elevated expression of activated NHE-1 induced a hypertrophic response.[61]

The hyperactivity of the NHE-1 is not restricted to the hypertension-induced model of CH, it has been demonstrated in several other forms of CH, in which its specific inhibition also resulted in the prevention/regression of hypertrophy. (for review see[62]).

Physiological cardiac hypertrophy and NHE-1

Both in human and animal studies it was demonstrated that certain factors are preferentially released during CH development, depending on the nature of stimuli (i.e. pathological or physiological).

The insulin like growth factor 1 (IGF-1) is increased during postnatal development as well as in response to exercise training.[63,64] Moreover, it has been reported that cardiac formation of IGF-1 (but not ET-1, big ET-1, and Ang II) is increased in athletes compared with healthy sedentary controls.[65] Moreover, studies in transgenic mice have confirmed the importance of IGF-1 signaling in physiological CH. In this sense, a mouse model overexpressing the IGF-1 receptor (IGF-1R) in the heart displayed physiological CH and a greater hypertrophic response to swim-training compared to control[66] while mice with cardiomyocyte specific knockdown of the same receptor were resistant to exercise-induced CH.[67] Moreover, inhibition of PI3K or genetic ablation of AKT1 prevented physiological CH[66,68,69] while overexpression of a constitutively active p110α PI3K resulted in physiological CH.[70]

Until 2014, the role of the NHE-1 in physiological CH had not been studied. We speculated that NHE-1 hyperactivity might also occur in exercise-induced CH since myocardial stretch, an activator of NHE-1, was also present in this type of CH. In line with this, we demonstrated for the first time that NHE-1 hyperactivity was prevented by an inhibitory AKT-dependent phosphorylation of the exchanger in a rat model of physiological CH induced by a swimming routine.[71]

Remodeling of pathological cardiac hypertrophy into a physiological one: ''switch on and switch off'' by NHE-1 activity

As it was already mentioned, the NHE-1 is hyperactive in the myocardium of the SHR[3,14] playing a key role in hypertrophy development through the increase in ([Ca^{2+}]i and calcineurin activation (Fig. 1).

Interestingly, in the SHR we have demonstrated that sustained exercise training is capable of transforming the hypertension-induced pathological CH into a physiological one, improving not only myocardial structure but also cardiac function at the time that calcineurin activity is normalized.[72]

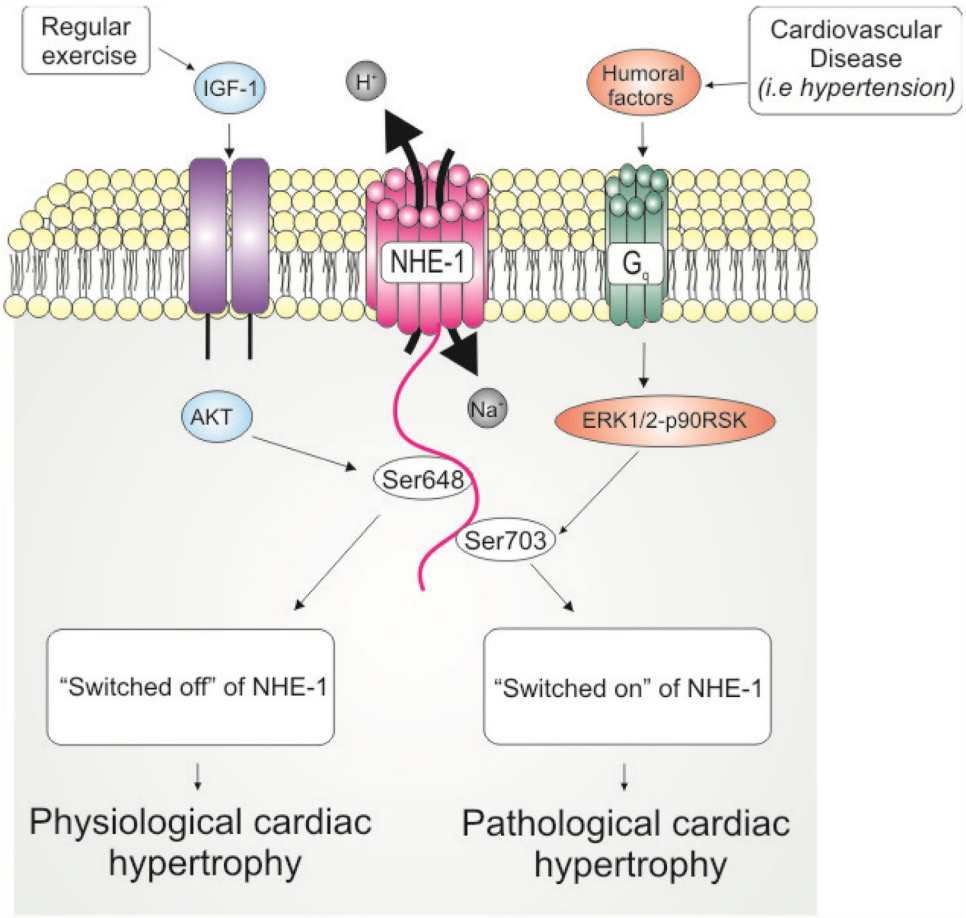

Figure 2 The NHE-1 represents a ''switch on/off'' for pathological CH development. When it is hyperactive, mainly through the phosphorylation of serine 703, is ''switched on'', with the consequent rise in $[Ca^{2+}]_i$ and calcineurin activation, leading to pathological remodeling. On the contrary, in the presence of AKT-mediated phosphorylation of serine 648, hyperactivity of the exchanger is prevented (''switch off'') and physiological CH develops.

NHE-1 inhibition as a potential therapeutic strategy

Pharmacological NHE-1 inhibitors

Extensive amounts of data coming from preclinical studies demonstrate that pharmacological inhibition of NHE-1 is cardioprotective. Several animal models of pathological CH (in vivo models of pressure overload in rabbits,[73] rats[8,74,3,33] and mice[75]; SHR; myocardial infarction[76]; isolated myocytes,[77–80] transgenic models,[5] cardiomyopathy[12]) have been used to demonstrate that pharmacological inhibition of NHE-1 is effective to prevent or induce the regression of cardiac remodeling. Interestingly, it was not reported any adverse effect in these experimental models in contrast to the increase in mortality due to cerebrovascular events reported in one clinical study.[81] The reason for this discrepancy constitutes an interesting question that remains to be answered.

Several NHE-1 inhibitors were developed with the goal of cardioprotection (Table 1). Amiloride, a sparing K^+ diuretic was the first compound proposed to inhibit the exchanger. Amiloride derivatives were synthesized in order to improve the potency and selectivity to inhibit the NHE-1 isoform. Among these, one widely used was EIPA (ethylisopropil amiloride), that has its half maximal inhibitory concentration (IC50) around 100 times smaller than that of amiloride and less action on Na+ channels and NCX. Further investigations led to benzoylguanidines such as HOE-694, HOE-642 (cariporide), EMD96785 (eniporide), BIIB-513, BIIB 723, EMD 87580 and other chemically related compounds such as SM-20550 and zoniporide (CP-597396). The IC50 of most of the newly developed compounds is of the same order of magnitude as EIPA, but with much higher selectivity for the NHE-1. These compounds differ in their solubility, the possible routes of administration and persistence of the effect after the washout of the drug.

Inspired in the impressive results in experimental models preventing or reducing CH with NHE-1 inhibitors, clinical studies were designed to explore these effects in humans. Only the EXPEDITION[81] and a subgroup of the GUARDIAN[82] clinical trials reported positive results. Unfortunately, the EXPEDITION study was prematurely stopped because of an increased mortality in the cariporide-receiving group due to cerebrovascular events.

A possible explanation for these findings is that systemic pharmacologic inhibition usually affects not only the

intended target but also some related or unrelated proteins in many tissues, being these putative responsible for the unwanted effects. Current pharmacological inhibitors are not highly selective for isoforms, therefore the inhibitors evaluated not only affect NHE-1 activity but also extend to other isoforms increasing the possibilities of non-desire effects. Another possible explanation for the unwanted effects could be that the specific inhibitors of the exchanger not only suppress the hyperactivity of the exchanger but also its basal activity, interfering with its normal function.

Genetics strategies to prevent NHE-1 hyperactivity

The already mentioned unwanted effects of NHE-1 pharmacologic inhibition paved the way to other strategies to prevent the exchanger hyperactivity and harmful consequences. In this sense, during the last years small interfering RNA against the NHE-1 delivered by intramyocardial injection of a lentivirus was used to prevent CH development in SHR.[83] These authors demonstrated that thirty days after the lentivirus injection, myocardial NHE-1 protein expression was reduced ~53%, without affecting the expression in other organs at the time that CH was significantly reduced. Similarly to what happened with pharmacologic inhibition of the NHE-1, no significant reduction in blood pressure was detected. Interestingly, despite the increased in wall tension, left ventricular midwall shortening was not modified suggesting an improvement in cardiac function. This strategy has been recently confirmed in a different experimental model of pathological CH.[84,85] Therefore, partial myocardial silencing of NHE-1 emerges as a promising tool for the treatment of pathological CH avoiding potentially undesired effects derived from a body-wide inhibition of NHE-1.

Exercise or AKT phosphorylation as potential therapeutic strategy

Several studies have demonstrated that regulating NHE-1 phosphorylation has beneficial effects against pathological CH.[86]

Recently, it has been demonstrated that the new SGLT2 inhibitors exert a direct effect on the cardiac NHE-1, possibly by occupying the Na^+-binding site.[87] As a consequence, the Na^+ influx to the cell is reduced. This novel and unexpected effect probably explains, at least in part, the impressive beneficial effect of these drugs on cardiovascular morbidity and mortality in diabetic patients.[87,88]

On the other hand, in 2009 we have demonstrated that a swimming routine was able to remodel pathological CH into the physiological phenotype, improving cardiac function and normalizing calcineurin activity.[72] More recently, we propose that IGF-1/AKT through preventing the NHE-1 hyperactivity and also exerting an antioxidant action could be responsible for these beneficial effects. More precisely, an AKT-dependent phosphorylation of the NHE-1 at serine 648, would be the event preventing the exchanger hyperactivity.[89]

Conclusion

The NHE-1 seems to act as a ''switch on/off'' for CH, leading to pathological remodeling when it is hyperactive, or to physiological growth when its activity is maintained under normal parameters (Fig. 2). In other words, AKT-mediated phosphorylation of the NHE-1 at serine 648 limits NHE-1 activity under conditions of hemodynamic overload that could otherwise result in the exchanger hyperactivity with the consequent rise in $[Ca^{2+}]_i$ and calcineurin activation. The prevention of NHE-1 hyperactivity under this circumstance results in a physiological cardiac phenotype of adaptive and reversible ventricular remodeling.

Based on the findings described, the prevention of NHE-1 hyperactivity should be considered as a promising strategy to avoid not only pathological cardiac remodeling but also other cardiac pathologies in which the rise in intracellular sodium plays a key role.

Even though it is out of the scope of this review, strong evidence is also available supporting that NHE inhibition provides benefits after cerebrovascular ischemia.[90] Moreover, as described for the heart and brain, renal ischemia stimulates the activity of the NHE, specially the NHE-3 isoform, and its inhibition has beneficial effects.[90]

Unfortunately, the promising results obtained in animal studies using pharmacological inhibitors of the NHE-1 were not reproduced in clinical trials.[82,91] As we mentioned, the most recent study, the EXPEDITION, revealed myocardial benefits of cariporide treatment in patients with ischemic heart disease, but unfortunately and unexpectedly, the treatment was associated with significantly greater incidence of stroke.[81] Whether or not these adverse effects are common to all NHE-1 inhibitors or peculiar to cariporide is not apparent to us at present.

On the other hand, it has been proposed the possibility that NHE-1 inhibition could be deleterious under basal conditions while beneficial when it occurs after an acid load.[92,93] Therefore, further research is necessary to clarify the necessary conditions to establish NHE-1 inhibition as therapeutic strategy for the clinical practice.

Conflict of interest

None declared.

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