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Review

Stretch-elicited Na^+/H^+ exchanger activation: the autocrine/paracrine loop and its mechanical counterpart

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Abstract

The stretch of the cardiac muscle is immediately followed by an increase in the contraction strength after which occurs a slow force increase (SFR) that takes several minutes to fully develop. The SFR was detected in a wide variety of experimental preparations including isolated myocytes, papillary muscles and/or trabeculae, left ventricle strips of failing human myocardium, in vitro isovolumic and in vivo volume-loaded hearts. It was established that the initial increase in force is due to an increase in myofilament Ca^{2+} responsiveness, whereas the SFR results from an increase in the Ca^{2+} transient. However, the mechanism(s) for this increase in the Ca^{2+} transient has remained undefined until the proposal of Na^+/H^+ exchanger (NHE) activation by stretch. Studies in multicellular cardiac muscle preparations from cat, rabbit, rat and failing human heart have shown evidence that the stretch induces a rise in intracellular Na^+ ($[Na^+]_i$) through NHE activation, which subsequently leads to an increase in Ca^{2+} transient via reverse-mode Na^+/Ca^{2+} (NCX) exchange. These experimental data agree with a theoretical ionic model of cardiomyocytes that predicted an increased Na^+ influx and a concurrent increase in Ca^{2+} entry through NCX as the cause of the SFR to muscle stretch. However, there are aspects that await definitive demonstration, and perhaps subjected to species-related differences like the possibility of an autocrine/paracrine loop involving angiotensin II and endothelin as the underlying mechanism for stretch-induced NHE activation leading to the rise in $[Na^+]_i$ and reverse-mode NCX.

Keywords: Angiotensin; Endothelins; Na/Ca-exchanger; Na/H-exchanger; Stretch/m-e coupling

1. Introduction

There are intrinsic mechanisms in the heart by which it can adjust cardiac output to changes in hemodinamic conditions. The increase in ventricular end-diastolic volume (EDV) caused either by an increase in venous return or a rise in aortic resistance is immediately followed by an increase in the strength of the heartbeat. This rapid adaptation, known as the Frank–Starling mechanism, allows cardiac output to match venous return or remain constant even when the heart faces higher afterloads. Next, there is a further increase in force that takes several minutes to fully develop and allows the return of EDV towards baseline. These load- and time-dependent changes in heart contractility were reproduced in isolated ventricular strips by Parmley and Chuck in 1973 [1]. These authors showed that the sudden increase of cardiac muscle length leads to a rapid initial increase in twitch force followed by a second slower force increase over several minutes as exemplified in Fig. 1.

After the description by Parmley and Chuck [1] the SFR was detected in a wide variety of experimental preparations including isolated rat and guinea pig cardiomyocytes, [2,3] papillary muscles from cat, ferret and rabbit and rat trabeculae [4–9], in vitro isovolumic dog hearts [10,11], and in vivo volume-loaded canine hearts [12]. Although

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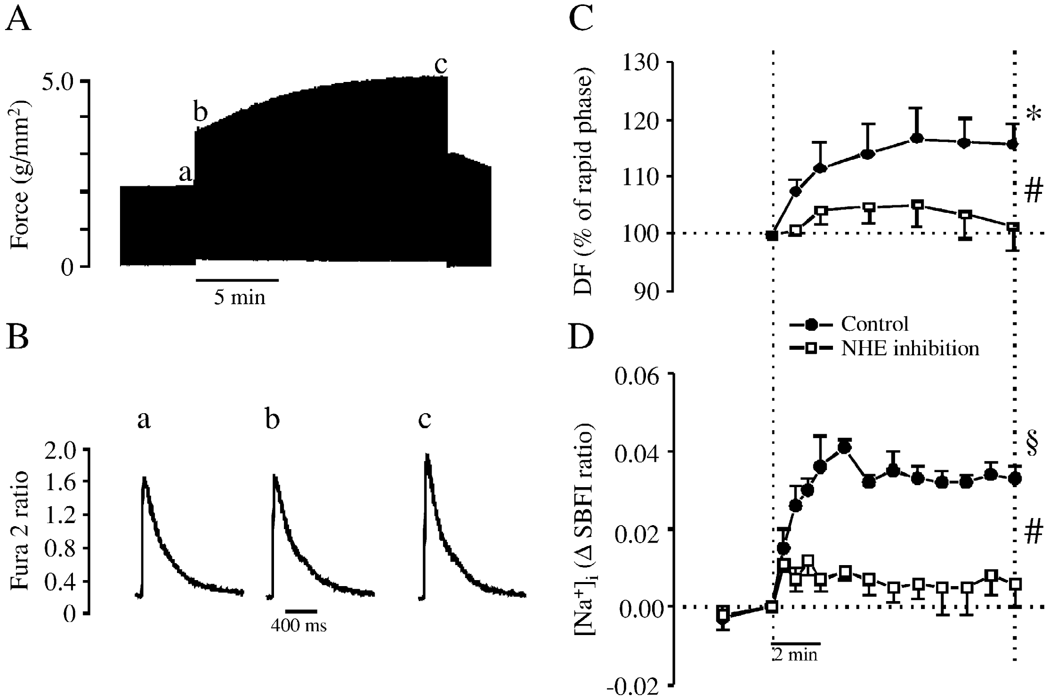

Fig. 1. Characteristic myocardial contractile response to a sudden increase in muscle length. After stretching a papillary muscle, there is an immediate increase in force (from a to b, panel A) due to an increase in myofilament Ca^{2+} responsiveness. After that, a progressive increase in force develops during the next 10–15 min, the SFR, that is due to an increase in the Ca^{2+} transient (panel B). This increase in Ca^{2+} transient is due to the increase in $[Na^+]_i$ (panel D, solid circles) caused by Na^+/H^+ exchange (NHE) activation since both the SFR and the increase in $[Na^+]_i$ are abolished by blocking NHE activity (panels C and D, open squares). $*$ indicates $P < 0.05$ vs. initial rapid phase. § indicates $P < 0.05$ vs. pre-stretched control, # indicates $P < 0.05$ between curves. (Adapted from Cingolani et al. [48] and from Alvarez et al. [6]).

one study in humans failed to detect the SFR after the elevation of EDV by intracardiac catheterization [13], the SFR was found to be present in failing human myocardium. Fig. 2 shows the characteristic biphasic force response to stretch in a left ventricular muscle strip isolated from an end-stage failing human heart. This observation in human myocardium is very much alike the functional response to stretch of a cat papillary muscle shown in Fig. 1, suggesting that the SFR to stretch is an ubiquitous intrinsic response of mammalian myocardium to mechanical load, even present in failing human myocardium.

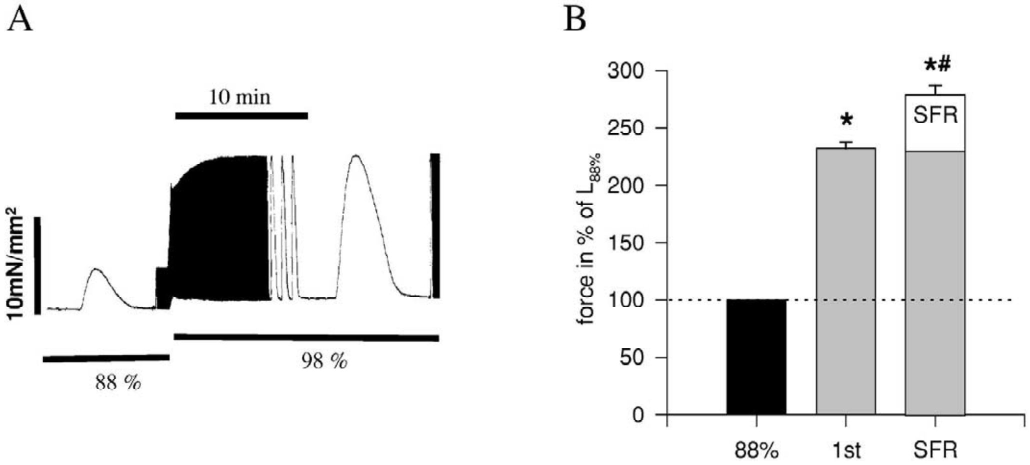

Fig. 2. The SFR is also present in failing human myocardium. A. Typical force record of the effect of stretch in a left ventricular muscle strip from an end-stage failing human heart. Stretch resulted in an immediate, followed by a slowly developing second phase in force increase. B. Overall results from eight independent experiments showing the relative contribution of the immediate force response vs. the SFR to the total force increase. (Pieske et al., unpublished results). $*$ indicates $P<0.05$ vs. 88%; # indicates $P<0.05$ vs 1st phase.

2. Mechanisms of the SFR to stretch

It has been established that the mechanisms that participate in each phase of the increase in force after stretch are quite different. There is general agreement that the initial rapid phase is due to an increase in myofilament Ca^{2+} responsiveness [14], with no change in the amount of Ca^{2+} delivered to the contractile elements. Instead, the SFR is the result of an increase in the Ca^{2+} transient (Fig. 1), a finding first reported by Allen and Kurihara in 1982 [4], and subsequently by several (including our) laboratories [2,5,6,10]. Even though the phenomenon received considerable attention, the mechanism responsible for the increase in the Ca^{2+} transient during the SFR was not completely defined and several alternatives were raised.

Increases in the Ca^{2+} transient might be accounted by increases in Ca^{2+} entry, decreases in Ca^{2+} efflux and/or changes in the sarcoplasmic reticulum (SR) Ca^{2+} handling. A main Ca^{2+} entry pathway in cardiac cells is the L-type Ca^{2+} current, which could be sensitive to stretch or affected by the prolongation of action potential duration induced by stretch [14,15]. So far, the experimental evidence is against a possible increase in Ca^{2+} entry through L-type channels as the cause of the augmented Ca^{2+} transients during the SFR. No change in L-type Ca^{2+} current after stretch was detected by Hongo et al. in isolated cardiomyocytes [2], nor was the SFR abolished by Ca^{2+} channel antagonists in the experiments by Chuck and Parmley performed in cat papillary muscles [16]. Besides the L-type Ca^{2+} current, stretch-activated ion channels might represent another potential Ca^{2+} entry pathway contributing to the enhancement of Ca^{2+} transient [17]. However, recent reports showed that gadolinium failed to modify the SFR in rabbit [8] and rat [18] papillary muscle.

Allen et al. [19] proposed the alternative that the increase of the Ca^{2+} transient might have resulted from an increase in Ca^{2+} influx that, increasing resting Ca^{2+} would load the SR and increase Ca^{2+} transients in subsequent beats.

The increase in Ca^{2+} binding to TnC immediately after the stretch [14] causes a decrease in Ca^{2+} transient. Trafford et al. [20] proposed that a decrease in Ca^{2+} transient causes a decrease in Ca^{2+} efflux that may load the SR. The greater loading of the SR will subsequently lead to the increase in the amplitude of the Ca^{2+} transient and force. Although a gain in the SR Ca^{2+} content was reported in rabbit myocardium [8,21] the studies of Kentish and Wrzosek [5], Bluhm and Levy [21], and Kentish et al. [22] would indicate that a functional SR is not a requirement for the development of the SFR since it can be elicited even in the presence of specific SR inhibitors. The appearance of an SFR in failing myocardium, a condition of severely depressed SR Ca^{2+}-ATPase activity [23,24], would also argue against a predominant role of the SR. In contrast, a report by Chuck and Parmley [16] described the reversal of the SFR in cat papillary muscles by caffeine; but changes in myofilament Ca^{2+} responsiveness promoted by caffeine could have interfered with their results. Despite the above mentioned studies showing that a functional SR is not mandatory for the development of the SFR, it was shown that the time-course of the SFR was delayed after SR inhibition [4,13].

Other mechanisms proposed to probably mediate the increase in Ca^{2+} transient were stretch-induced changes in intracellular second messengers. Increases in cAMP after stretch were reported in isolated ferret papillary muscles [9], and intact canine hearts [10], whereas increased production of $InsP_3$ was found in rat cardiomyocytes [25]. Also in isolated rat cardiomyocytes, Vila Petroff et al. [26] proposed that endogenous NO, released from stretched myocytes themselves, could act on ryanodine receptors, and thus enhance the SR Ca^{2+} releasing capacity. Though interesting, these results are difficult to reconcile with the aforementioned findings showing that the SFR is elicited even with non-functional SR.

3. Role of NHE and reverse-mode NCX in the development of the SFR

An alternative hypothesis for the increase in Ca^{2+} transient amplitude during the SFR emerged from the results in cat papillary muscles by Cingolani et al. [27] showing stretch-induced activation of the sarcolemmal Na^+/H^+ exchanger (NHE). Although this early study was not focused on the contractile response to stretch, subsequent work by the same group demonstrated the implication of NHE activation by stretch in SFR development. Their results showed a marked increase in intracellular Na^+ ($[Na^+]_i$) with a time-course similar to, or slightly preceding, the SFR and both the rise in $[Na^+]_i$ and SFR were abolished by NHE inhibitors (Fig. 1) [6,7]. Since the rise in $[Na^+]_i$ changes the thermodynamic balance of the Na^+/Ca^{2+} exchange (NCX), the possibility of an increase in Ca^{2+} influx through reverse-mode (Ca^{2+}_{in}–Na^+_{out}) NCX was proposed. The participation of this mechanism in the increase in Ca^{2+} transient and the generation of the SFR was further supported by the experiments of Pérez et al. [7] in cat papillary muscles. In these experiments, the authors demonstrated the suppression of the SFR after inhibition of the NCX either by extracellular Na^+ deprivation or with the NCX blocker KB-R7943 (Fig. 3). The involvement of the NHE and reverse-mode NCX in the SFR elicited by stretch in rabbit myocardium is also reported in this Spotlight issue by von Lewinski et al. [8]. In accordance with these results, preliminary experiments revealed a clear dependency of SFR on NHE and reverse-mode NCX activation in failing human cardiac tissue (Pieske et al. unpublished observation). Therefore, the increase in $[Na^+]_i$ induced by NHE activation is the underlying mechanism for the increase in Ca^{2+} transient and force. It may be

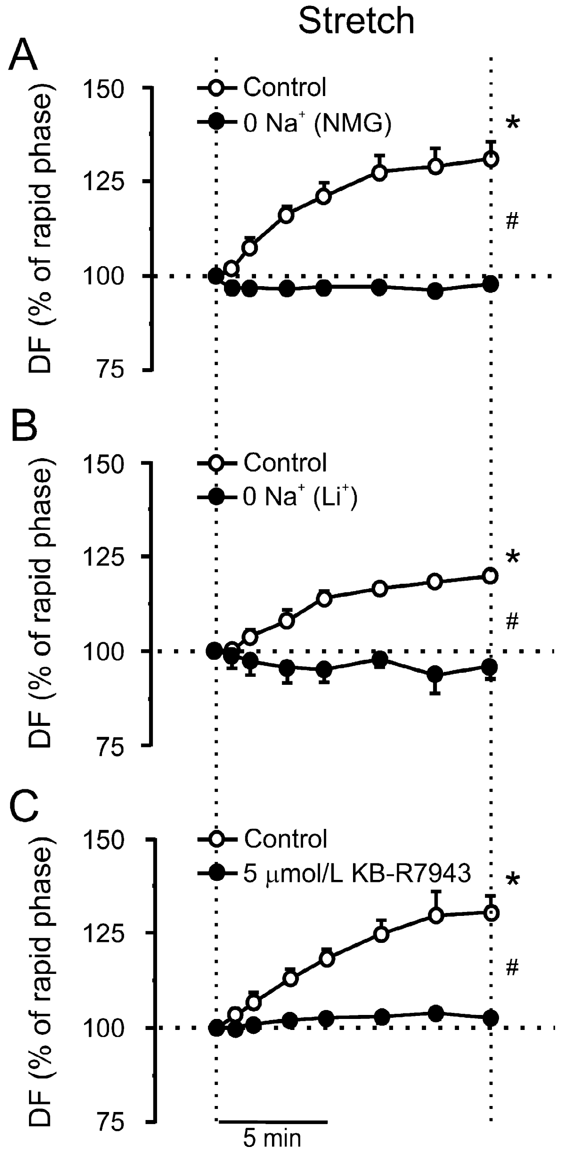

Fig. 3. Role of reverse-mode of NCX in the development of the SFR. The NCX operating in reverse-mode is a requirement for the development of the SFR since any maneuver inhibiting the reverse-mode NCX like extracellular Na^+ removal (panels A and B, solid circles) or KB-R7943 (panel C, solid circles) cancelled the SFR. (Adapted from Pérez et al. [7]).

argued that NHE activation should cause intracellular alkalinization. However, it is not the case when bicarbonate-dependent mechanisms are operative [6] because the simultaneous activation of the Na^+-independent Cl^-/HCO_3^- exchanger minimizes the change in pH_i [28]. In the absence of bicarbonate NHE activation raises pH_i, and under this condition the SFR results from a combination of two mechanisms: the increase in $[Na^+]_i$ leading to the increase in Ca^{2+} influx through reverse-mode NCX and the increase in myofilament Ca^{2+} responsiveness due to intracellular alkalosis. As a consequence, the magnitude of the SFR is almost doubled in the absence of bicarbonate and KB-R7943 reduces it by half [29].

A potential point of controversy could be how important is the rise in $[Na^+]_i$ for the development of the SFR. In light of the results in multicellular muscle preparations by Alvarez et al. [6] and Perez et al. [7] the increase in $[Na^+]_i$ appears to be mandatory (Fig. 1). Instead Hongo et al. [2] showed that the stretch did not promote an increase in $[Na^+]_i$ in isolated myocytes. It may be speculated that there is at least two mechanisms for the SFR: a $[Na^+]_i$-independent mechanism seen in isolated cardiomyocytes, and another one dependent on nonmyocyte cells of multicellular muscle preparations acting to increase $[Na^+]_i$. However, it should be noted that NHE and NCX have been found expressed colocalized along the transverse tubular system in cardiomyocytes [30,31]. Their close proximity probably enhances the effect of changes in $[Na^+]_i$ able to drive the reverse-mode NCX. Interestingly, an elegant theoretical ionic model was recently used by Bluhm et al. [32] to analyze the changes in the parameters of sarcolemmal ion fluxes that reproduced the effect of step changes in cardiac muscle length. The results suggested that the slow change in force that follows a sudden increase in muscle length may be caused by length-induced step changes in sarcolemmal Na^+ influx, leading to an increase in $[Na^+]_i$ and a concurrent increase in systolic Ca^{2+} entry through the NCX. Therefore, the theoretical model and the experimental results are in good agreement about a role of NHE and reverse-mode NCX in the development of the SFR.

4. Role of angiotensin II (Ang II) and endothelin in the SFR

The study by Cingolani et al. [27] in cat papillary muscles provided experimental evidence to support the participation of an autocrine/paracrine mechanism involving endogenous Ang II and endothelin in the activation of NHE and the SFR. Blockade of Ang II-AT_1 or endothelin ET_A receptors with selective inhibitors abolished stretch-induced NHE activation as well as the increase in the Ca^{2+} transient and the SFR (Fig. 4). Coincidentally, Calaghan and White recently reported that the blockade of endothelin ET_A receptors reduced the SFR by half in ferret papillary muscle [33], but they were unable to demonstrate a contribution of Ang II. In contrast, blockade of AT_1 and ET_A receptors failed to affect the SFR in rabbit papillary muscle [8]. Therefore, although NHE activation seems to be responsible for the development of the SFR, the mechanism through which NHE is activated remains controversial.

A relevant aspect is to define, in relation to the proposed activation of the renin–angiotensin and endothelin systems, if it occurs in sequential steps of a single process or they are independently activated by stretch. There is an increasing body of evidence showing that many effects thought to be due to Ang II are actually the result of endogenous endothelin. The mediation of endothelin in

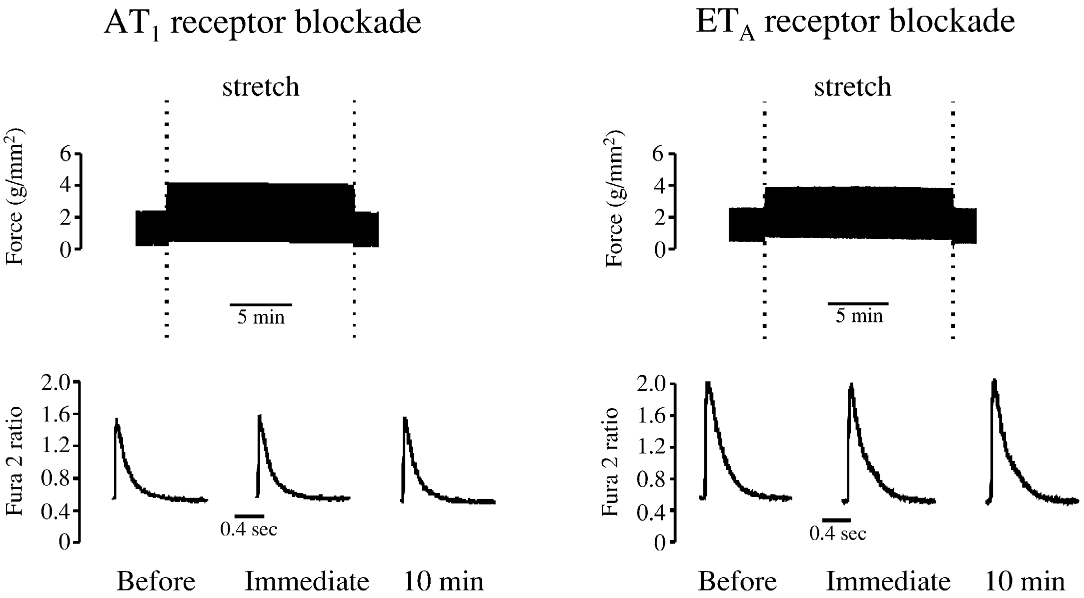

Fig. 4. The SFR is the mechanical counterpart of an autocrine/paracrine mechanism triggered by the stretch that involves AngII-endothelin release. Both the increase in Ca^{2+} transient and the SFR to stretch are cancelled by the blockade of Ang II-AT_1 receptors with losartan (left panels) or endothelin ET_A receptors with BQ 123 (right panels). (Adapted from Alvarez et al. [6]).

great variety of Ang II effects such as its hypertensive action [34], induction of hypertrophy in both cardiac myocytes exposed to mechanical stress [35–37] and transgenic hypertensive rats [38], and activation of membrane transport mechanisms [27,39], has been reported. In connection with this, a recent study by Aiello et al. [40] reported that the increase in outward NCX current (I_{NCX}) produced by exogenous Ang II in isolated cat cardiomyocytes was cancelled by blocking either Ang II-AT_1 or ET-1 receptors (Fig. 5).

Another important aspect to be considered is the origin of Ang II and endothelin in stretched myocardial preparations. Even though it is known that myocardial cells have local renin–angiotensin [41] and endothelin systems [42], and that the stretch stimulates the secretion of Ang II [36,43,44] and endothelin [44], most of the knowledge about the events that couple mechanical stress with intracardiac peptide secretion and/or production has come from studies performed in isolated neonatal myocytes. Papillary muscles are multicellular with cardiomyocytes being surrounded by various cells, mainly fibroblasts and endothelial cells, which also release endothelin [45]. Whether cardiomyocytes themselves or any other type of intramyocardial cells are the source of endothelin is unknown at present. In cat papillary muscle, Pérez et al. [7] demonstrated that the SFR was preserved after rendering nonfunctional vascular and endocardial endothelial cells, whereas Calaghan and White [33] showed that the removal of endocardial endothelial cells reversed the slow response to stretch. We do not have a clear explanation for the discrepancy besides the simplistic one about species-related differences. Pioneering studies by Sadoshima et al. [43] established that the mechanical stretch caused the release of preformed Ang II to the surrounding medium of cultured neonatal rat cardiomyocytes but not in nonmyocyte cultures. These authors also showed that Ang II acted as the initial stimulus of the stretch-induced hypertrophic response. Further elucidation of the process came from the experiments mentioned above by Ito et al. [35] who showed in cultured isolated myocytes that Ang II causes a PKC-dependent increase in prepro endothelin-1 mRNA levels and release of endothelin-1. The experiments by Aiello et al. previously cited [40] in isolated cat cardiomyocytes also provided evidence favoring the pro-

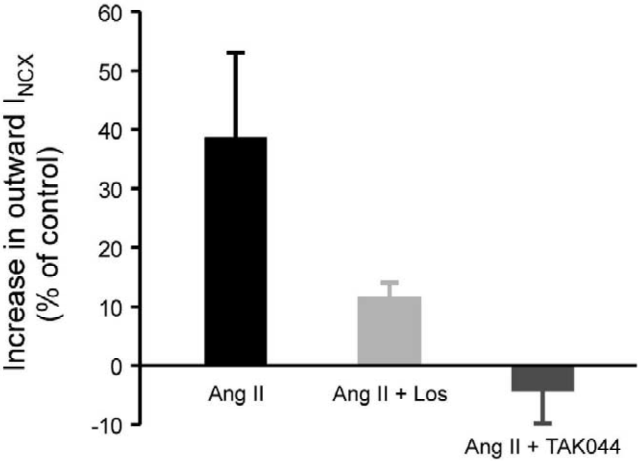

Fig. 5. Ang II increases outward I_{NCX} through AT_1 receptors in isolated myocytes. The effect of exogenous Ang II increasing outward I_{NCX} is cancelled after the blockade of endothelin receptors with TAK044 indicating that Ang II-effect is mediated by endogenous endothelin. The results also indicate that cardiomyocytes themselves are at the same time, source and target of endothelin. (Adapted from Aiello et al. [39].

posal that myocytes themselves are both the source and the target of endothelin.

As a consequence of the peptide release, multiple downstream signal transduction pathways are activated, including phospholipases C, D and A_2, as well as many types of protein kinases, such as PKC and MAP kinase cascades [43,44,46]. The study by Yamazaki et al. [44] also showed that whereas ion channels inhibitors like gadolinium, streptomycin, glibenclamide or CsCl did not have any inhibitory effect, NHE blockade could partially attenuate MAP kinase activation and protein synthesis induced by stretch. However, these investigators have called recently the attention to the fact that stretch can trigger myocyte growth through Ang II-independent pathways in addition to the autocrine/paracrine mechanism [46,47]. In this context, Cingolani and collaborators provided a link between the molecular events and contractile effects triggered by myocardial stretch as it is schematized in Fig. 6. The phenomenon of myocardial response to mechanical stress can, therefore, be viewed as a complex mechanism, which through a combination of responses (increase in force and hypertrophy) meets the common end-point of how to face an increased hemodynamic load. However, we should consider that although the activation of NHE first proposed by Cingolani and collaborators [6,27] to be the mechanism underlying the SFR has been confirmed by other laboratories [8,44], the pathway for this activation remains controversial and perhaps it is subjected to species-dependent differences.

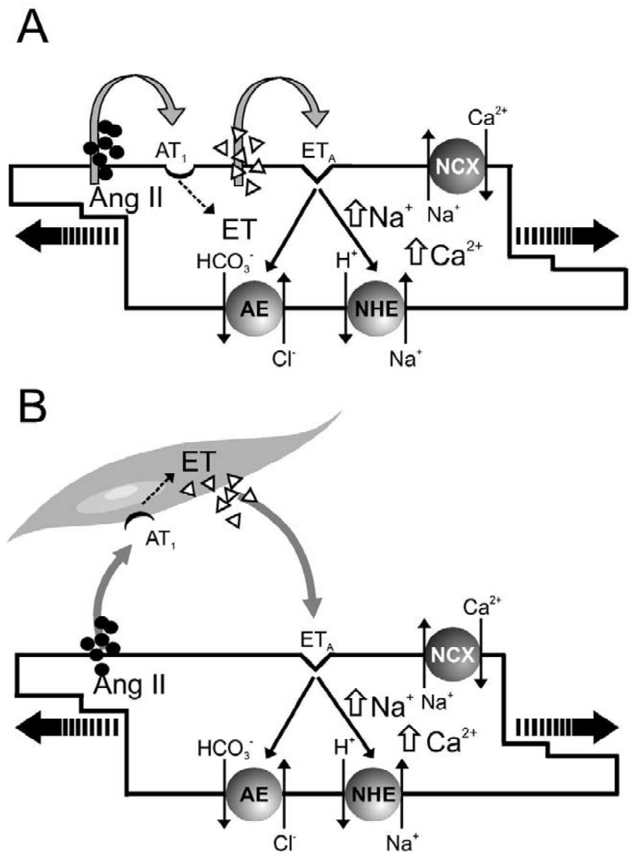

Fig. 6. Schematic representation of the autocrine/paracrine proposed loop. Upon myocardial stretch, preformed-stored Ang II is released from cardiomyocytes; this peptide either acting on the cardiomyocyte (autocrine mode, panel A) or other intramyocardial type of cells, namely fibroblasts and/or endothelial cells in a pracrine mode (panel B), will induce endothelin (ET) release. In turn, ET, through ET_A receptors will induce NHE activation, leading to an increase in $[Na^+]_i$ and Ca^{2+} transient through reverse-mode NCX. (Adapted from Pérez et al. [7]).

5. Conclusions

The SFR seems to be a general phenomenon intrinsic to the mammalian myocardium. This functional response appears to be mediated by stretch-dependent activation of NHE and a consecutive, $[Na^+]_i$-dependent Ca^{2+} transient increase mediated through reverse-mode NCX. This slowly developing inotropic response may serve as an additional physiological mechanism to adapt stroke volume to increases in hemodynamic load even in the failing human heart. However, a number of questions remain unanswered: is it the only pathway elicited by stretch with implication in cardiac hypertrophy; or, as proposed by Yamasaki et al., could there be parallel Ang II-dependent and independent mechanisms? If endothelin is involved, which subtype of receptors (ET_A or ET_B) are involved? Is it necessary to stimulate both of them for the NHE activation? How does stretch cause the release of peptides, and which is the mechanosensor? How important are these mechanisms for determining cardiac hypertrophy? An attractive hypothesis would be that the chain of events leading to the increase in $[Ca^{2+}]_i$ could elicit cardiac hypertrophy through Ca^{2+}-calmodulin–calcineurin-dependent pathways. The fact that the interruption of this chain of events by inhibition of NHE activity decreases cardiac hypertrophy [49,50] seems to support the hypothesis.

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