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# The Effect of pH on Na-Ca Exchange in Atrial Myocytes of Rabbit

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= Abstract =In atrial trabeculae and single atrial cells, we examined the effect of pH on the Na-Ca exchange mechanism. In atrial trabeculae both acidic and alkaline pH reduced Na-free contracture. Inward current of Na-Ca exchange activated by repolarizing pulse after a brief depolarizing pulse to +40 mV for 2 ms from the holding potential of −70 mV in single atrial cells was reduced by acidic pH, and enhanced by alkaline pH. Amiloride, which causes intracellular acidosis, reduced Na-Ca exchange current and 20 mM $NH_4Cl$ (intracellular alkalosis)-enhanced Na-Ca exchange current. From the above results, it was concluded that the effect of pH on forward and reverse modes of Na-Ca exchange might not be symmetric.

Key words: ***Na-Ca exchange, Na-free contracture, pH, Rabbit atrium.***

## INTRODUCTION

Since the original observations by Gaskell (1880), both the negative inotropic effect of acidosis and the positive inotropic effect of alkalosis on heart muscle have been well documented. The intracellular acidosis could be a cause for the decrease of contractility observed during myocardial ischemia (Cobbe and Poole-Wilson 1980; Katz and Hecht 1969; Steenbergen *et al.* 1977).

The cardiac contractility is closely related to intracellular Ca ($[Ca]_i$) which is affected by the Ca influx, Ca extrusion, Ca release from and Ca reuptake by sarcoplasmic reticulum (SR) (Noble 1984). The Ca extrusion may occur through either Ca-pump or Na-Ca exchange mechanism. The cardiac sarcolemmal Ca-pump seems to contribute little to the Ca extrusion because it saturates at low Ca concentration and the rate of Ca extrusion by Ca pump is slow (Caroni and Carafoli 1981). On the other hand, Na-Ca exchange plays an important role in regulating $[Ca]_i$. Na-Ca exchange mechanism has two modes (Kimura *et al.* 1987). The forward mode is $[Na]_0$-dependent Ca efflux which can be recorded electrophysiologically as an inward current, decreases as membrane becomes depolarized and contributes to lowering the $[Ca]_i$ and maintaining the plateau. The reverse mode is $[Na]_i$-dependent Ca influx which can be recorded as an outward current, increases as membrane becomes depolarized and contributes to raising the $[Ca]_i$.

The change in pH can influence many Ca-dependent processes. It has been reported that the acidic pH inhibited $Na_0$-dependent Ca efflux in the squid giant axon (Dipolo and Beauge 1982), inward current of Na-Ca exchange in the rod cell (Hodgkin and Nunn 1987), Na-free contracture (Chapman and Tunstall 1980) which occurs with $Na_i$-dependent Ca influx (Chapman 1974; Kim 1987) and both forward and reverse mode of Na-Ca exchange in cardiac sarcolemmal vesicle (Philipson *et al.* 1982), while alkaline pH enhanced $Na_0$-dependent Ca efflux at squid giant axon, in-

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ward current of Na-Ca exchange in rod cell, two modes of Na-Ca exchange in cardiac sarcolemmal vesicle and Na-free contracture in frog ventricle. However, there was a controversial result about pH effect on Na-Ca exchange. Earm and Irisawa (1986) reported that both acidosis and alkalosis inhibited outward current of Na-Ca exchange in single ventricular myocytes of guinea-pig.

Thus we investigated the effect of pH on the Na-Ca exchange mechanism in two modes. To study forward mode we recorded the inward current of Na-Ca exchange activated by repolarizing pulse after a brief depolarizing pulse to −40 mV for 2 ms from holding potential −70 mV (Earm *et al.* 1989). Reverse mode of Na-Ca exchange was tested by Na-free contracture (Chapman 1974; Chapman and Tunstall 1980; Kim 1987).

## MATERIALS AND METHODS

### Preparation of Atrial Trabeculae and Single Atrial Cells:

Young rabbits of either sex weighing about 1 Kg were used in the present study. Animals were stunned and bled. Chest was opened, and the heart was removed quickly and transferred into a dissection chamber containing oxygenated Tyrode solution. To get atrial trabeculae the atria were separated from the rest of the heart and cut open through the superior and inferior vena cava to expose the right atrium and sinoatrial node. After a recovery period of one hour, free atrial trabeculae were tied at two ends using fine cotton thread and isolated from the atria.

Single atrial cells of rabbit were isolated by a method similar to that described by Kimura *et al.* (1987). Briefly the heart was perfused with low Ca-Tyrode solution (30-50 $\mu$M Ca) containing collagenase (0.08 mg/ml, Yakurutu) for 10-15 min on Langendorff perfusion system. Atrial tissue was dissected out and mechanically agitated to disperse the cells and then stored in low-Cl, high-K medium at 4°C.

### Solutions:

In experiments of atrial trabeculae, normal Tyrode solution contained (in mM): NaCl 140, KCl 3, $CaCl_2$ 2, $MgCl_2$ 1, glucose 5. The pH was adjusted to 7.4 at 37°C with 5 mM Tris-HCl. In all experiments, $10^{-6}$ M of ouabain which is enough to inhibit the Na-K-ATPase activity was pretreated to increase the intracellular $Na^+$. Na-free solution was made by replacing NaCl isosmotically with Tris-Cl. The various pH solutions were made by Tris or HEPES buffers.

In experiments on single atrial cells, the solution used to superfuse atrial cells contained (in mM): NaCl 140, KCl 5.4, $CaCl_2$ 1.8, $MgCl_2$ 1, $NaH_2PO_4$ 0.33, glucose 5, HEPES 5. The pH was adjusted to 7.4 with NaOH. The internal perfusing solution contained (in mM): K-aspartate 110, Mg-ATP 5, diTris-creatine phosphate 5, $MgCl_2$ 1, KCl 20, HEPES 5, EGTA 0.1. The internal pH was adjusted to 7.4 with KOH.

Ouabain, amiloride and all other chemicals and drugs used in this study are from Sigma.

### Experimental Setup:

In experiments on atrial trabeculae, tissues were allowed to relax in the horizontal chamber for at least 1 hour. Contraction was recorded with a force transducer (Device force transducer).

In experiments on single atrial cells, the cells were voltage-clamped using whole cell patch clamp apparatus (List, EPC-7) according to the original technique developed by Hamill *et al.* (1981). Glass electrodes with resistances of 2-3 M$\Omega$ were used. During the experiments, cells were superfused (1 ml/min) at 35°C. The data were recorded on a PCM data recorder (NF, 880) for future analysis. Data were also displayed on a digital oscilloscope (Hitachi, 6041) and pen recorder (Harvard oscillogragh) and could then be directly reproduced onto an X-Y recorder (Graphtec, WX 2400).

## RESULTS

### The Effect of $pH_0$ on the Na-Free Contracture

The first series of experiment was conducted to study the effects of varying extracellular pH ($pH_0$) on the Na-free contracture. Since the Na-free contracture can be developed during the condition of high intracellular Na concentration, $10^{-6}$ M of ouabain, which inhibits Na-K pump completely, was pretreated to increase intracellular $Na^+$. When the $pH_0$ was changed from 7.4 to 6.0 the peak tension of Na-free contracture was decreased to almost the half of the

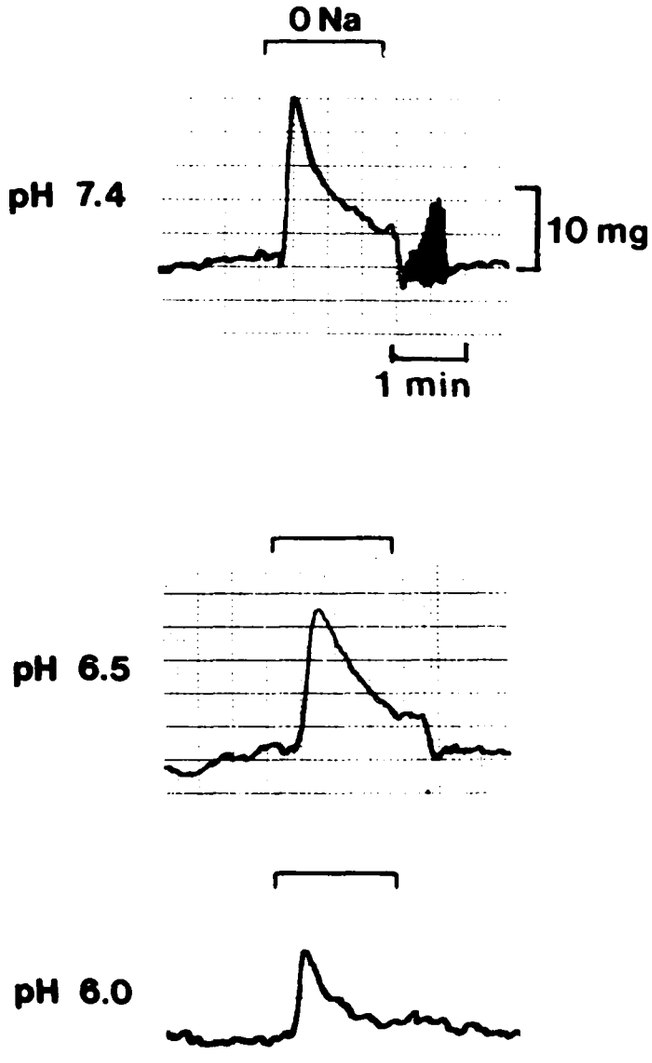


Fig. 1. The effect of external acidic pH on Na-free contracture. Lowering the external pH from 7.4 to 6.0 decreased the amplitude of the Na-free contracture. $10^{-6}$ M ouabain which inhibits Na-K pump, was pretreated to increase intracellular $Na^+$.

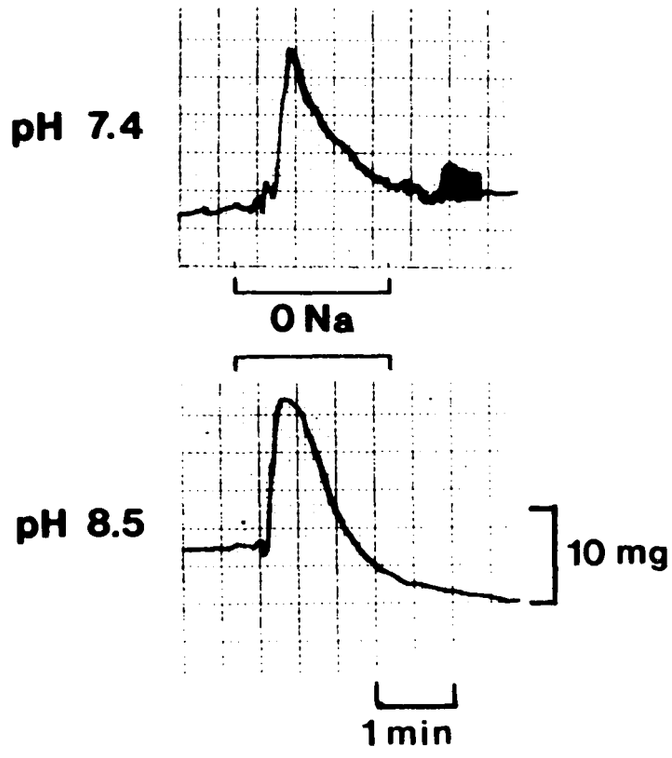


Fig. 2. The effects of external alkaline pH on Na-free contracture. Raising the external pH from 7.4 to 8.5 decreased the amplitude to Na-free contracture. $10^{-6}$ M ouabain was pretreated to increase intracellular $Na^+$.

value at pH 7.4 (Fig. 1). Simultaneously, the basal tone and the time taken for relaxation to 50 % (half relaxation time) decreased also. Raising the $pH_0$ from 7.4 to 8.5 decreased the peak tension of Na-free contracture (Fig. 2) and increased the basal tone and the half relaxation time.

The averaged effects of $pH_0$ on the basal tone, peak tension and total peak tension of Na-free contracture are shown in Fig. 3. The amplitude of peak tension at $pH_0$ 7.4 were taken as 100 %, and the amplitudes at various pHs were presented by % values relative to the amplitude of peak tension at pH 7.4. The amplitude values of basal tone were -43 % at pH 5.0, −15 % at pH 6.0, −4 % at pH 6.4 and 54 % at pH 8.5. The amplitude values of peak tension were 43 % at pH 5.0, 63 % at pH 6.0, 83 % at pH 6.4 and 68 % at pH 8.5.

### The Effects of $pH_i$ on the Na-Free Contracture

The intracellular acidification was induced by superfusing with solutions saturated with 5 % $CO_2$-95 % $O_2$ mixture. The intracellular acidosis decreased basal tone progressively while the peak tension and the half relaxation time were increased. Fig. 4 represents a typical example. As shown in Fig. 5 the intracellular alkalinization induced by 20 mM $NH_4Cl$ decreased the basal tone and half relaxation time, but peak tension was potentiated during alkalosis.

### The Effects of Internal and External pH on the Na-Ca Exchange Current

As already mentioned in Methods, Na-Ca exchange current was activated by the repolarizing pulse after a brief depolarizing pulse to +40 mV

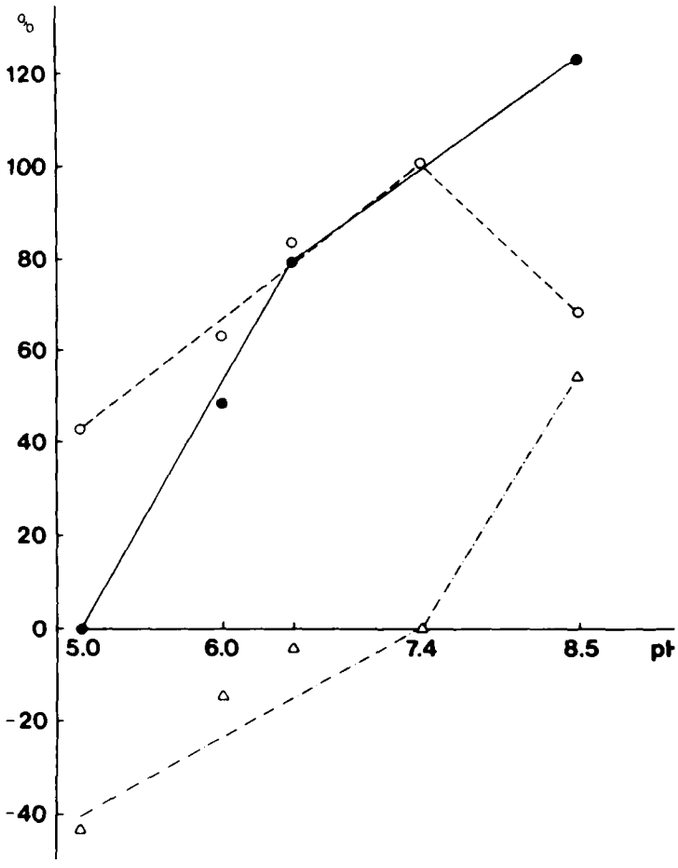


Fig. 3. The effects of external pH on basal tone, peak tension and total peak tension of Na-free contracture. The amplitude of peak tension at $pH_0$ 7.4 was taken as 100 %, and the emplitudes at increased or decreased $pH_0$ were presented by % values relative to the amplitude of peak tension at $pH_0$ 7.4. Open triangle (△): basal tone; open circle (○): peak tension; filled circle (●): total peak tension.

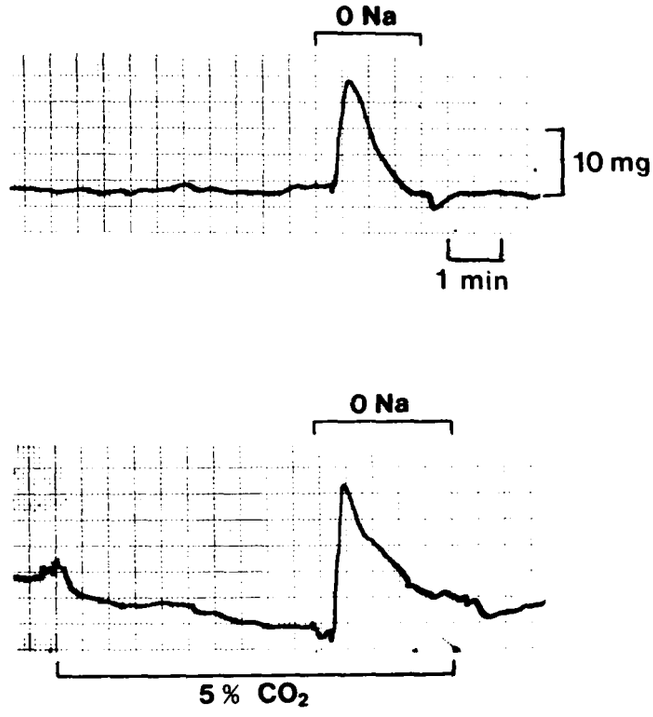


Fig. 4. The effects of acidic $pH_i$ on Na-free contracture. the intracellular acidosis induced by 5 % $CO_2$ increased the peak tension of Na-free contracture and decreased the basal tone. $10^{-6}$ M ouabain was pretreated to increase intracellular $Na^+$.

for 2 ms from the holding potential of −70 mV. Peak level of inward current was usually obtained in 5 ms and its amplitude at −70 mV was in the range −200 to −500 pA.

Fig. 6 represents examples of Na-Ca exchange current traces obtained by changing the external pH. When the extracellular pH was changed from 7.4 to 6.0, the Na-Ca exchange current decreased markedly (Fig. 6A) while change in extracellular pH from 7.4 to 8.0 enhanced Na-Ca exchange current (Fig. 6B). Internal acidification with 5 % $CO_2$ reduced Na-Ca exchange current and internal alkalinization with 20 mM $NH_4Cl$ enhanced Na-Ca exchange current (Fig. 7). Na-Ca exchange current was decreased by 1 mM amiloride which causes intracellular acidosis due to inhibition of Na-H exchange (Fig. 8A). Na-Ca exchange current enhanced by 20 mM $NH_4Cl$ (internal alkalinization) was reduced to control level by 1 mM amiloride (Fig. 8B).

## DISCUSSION

It is well known that contractility of the heart muscle is reduced during perfusion with acidic fluids and is increased in alkaline solutions. The cardiac contractility is closely related to intracellular Ca which is controlled by the Ca influx, Ca extrusion, Ca release from and Ca reuptake by sarcoplasmic reticulum (Noble 1984). Changes in pH can affect many Ca-dependent processes, i.e. Ca-channel in the heart (Chesnais *et al.* 1975; Irisawa and Sato 1986; Kohlhardt *et al.* 1976; Sato *et al.* 1985), Na-dependent Ca efflux in the squid giant axon (Dipolo and Beauge 1982), inward current of Na-Ca exchange in rod cell (Hodgkin and Nunn 1987), the Na-Ca exchange in cardiac sarcolemmal vesicles (Philipson *et al.* 1982), Na-free contracture in

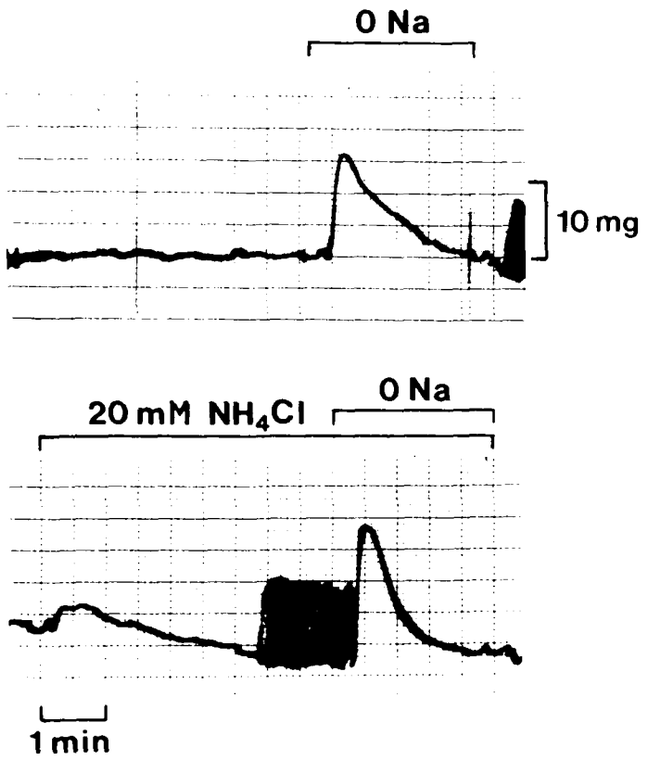


Fig. 5. The effects of alkaline $pH_i$ on Na-free contracture. Intracellular alkalinization induced by 20 mM $NH_4Cl$ caused a slight potentiation of Na-free contracture and decreased basal tone. $10^{-6}$ M ouabain was pretreated to increase intracellular $Na^+$.

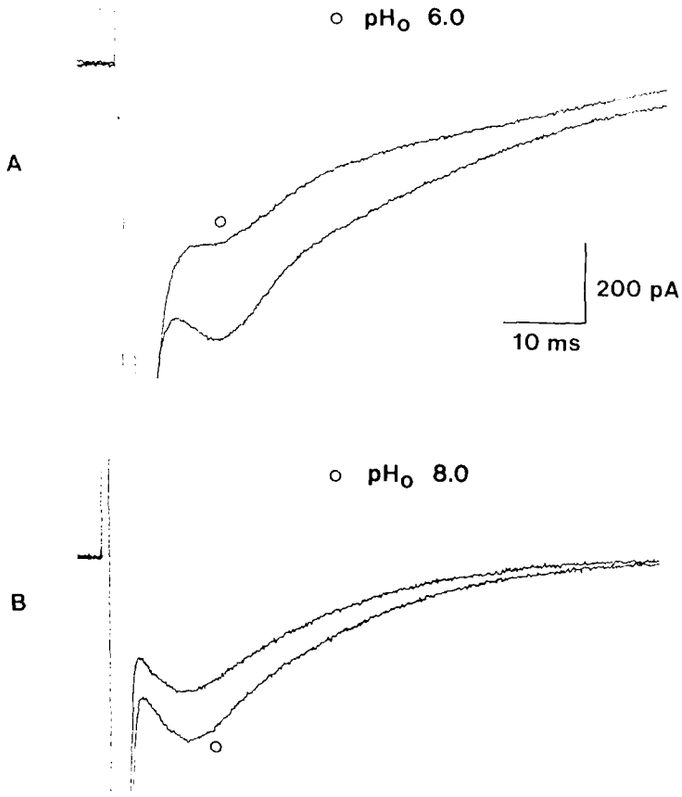


Fig. 6. The effects of external pH on Na-Ca exchange current. Na-Ca exchange current was activated by voltage-clamp pulse preceded by the pulse to +40 mV for 2 ms from the holding potential of −70 mV. Change in pH from 7.4 to 6.0 reduced Na-Ca exchange current (A) and change from 7.4 to 8.0 enhanced Na-Ca exchange current (B).

frog ventricle (Chapman and Tunstall 1980) and outward current of Na-Ca exchange in single ventricular cells of guinea-pig (Earm and Irisawa 1986). It is also considered that pH is not the main factor being involved in triggering or inactivation of Ca release from SR (Fabiato 1985) but modifies Ca uptake by SR (Fabiato 1985; Fabiato and Fabiato 1978; Nakamura and Schwartz 1972).

### The Effects of pH on the Na-Free Contracture

It has been suggested that Na-free contracture is occurred either by the suppression of forward mode, i.e. $Na_0$-dependent Ca efflux, or by the enhancement of reverse mode, i.e. $Na_i$-dependent Ca influx (Chapman 1974; Kim 1987). The mechanism of spontaneous relaxation of Na-free contracture is, on the other hand, still unclear but possible explanations might be the decrease in $Na_i$ (Chapman 1974) or direct action of $H^+$ on SR (Somlyo *et al.* 1981). In the present study, unlike frog ventricle (Chapman and Tunstall 1980), external alkalinization and acidification reduced Na-free contracture. It agrees well with the effect of $pH_0$ on outward current of Na-Ca exchange in single ventricular cells of guinea-pig (Earm and Irisawa 1986) if Na-free contracture is assumed to be occurred by the increase in $Na_i$-dependent Ca efflux (Chapman 1974). However, internal acidification and alkalinization increased Na-free contracture while internal acidification and alkalinization reduced outward current of the Na-Ca exchange. The possibile reasons for the difference of these effects may be the followings: i) the effects of $pH_i$ on the sensitivity of myofilaments to Ca (Chapman and Tunstall 1980), Ca uptake by SR (Fabiato 1985; Fabiato and Fabiato 1975) and intracellular

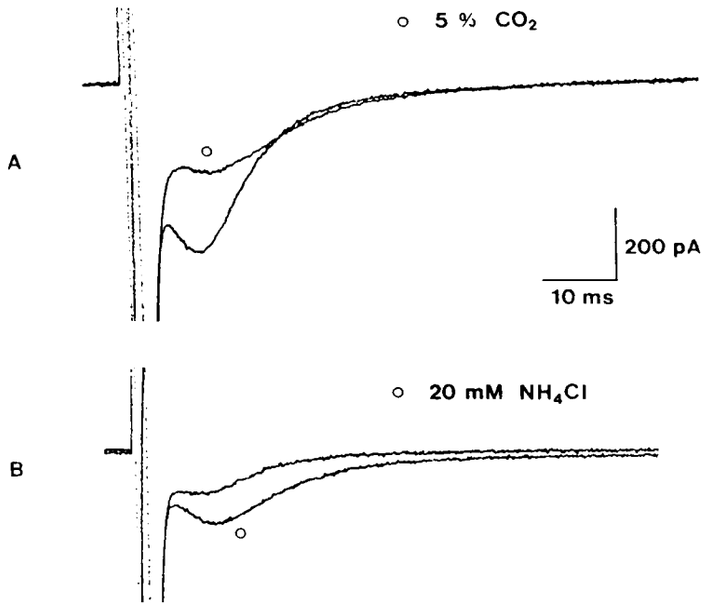


Fig. 7. The effect of internal pH on Na-Ca exchange current. Internal acidification by 5 % $CO_2$ reduced Na-Ca exchange current (A) and alkalinization by 20 mM $NH_4Cl$ enhanced Na-Ca exchange current (B).

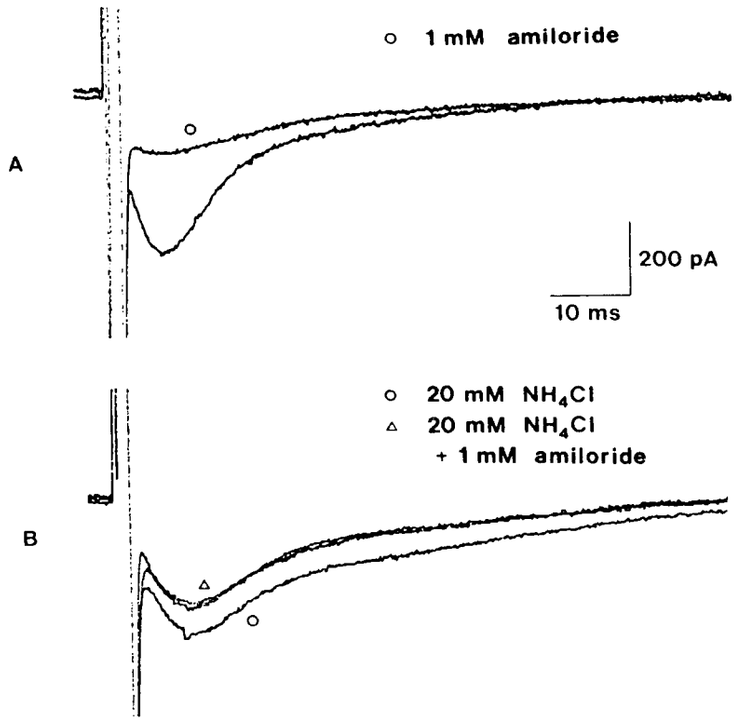


Fig. 8. The effect of amiloride on Na-Ca exchange current. 1 mM amiloride which causes intracellular acidosis due to inhibition of Na-H exchange reduced Na-Ca exchange (A) and Na-Ca exchange current enhanced by 20 mM $NH_4Cl$ (B).

Ca (Kim and Smith 1988), ii) the effects of $pH_i$ on Na-free contracture was studied with 5 % $CO_2$ or $NH_4Cl$, while the effect of $pH_i$ on outward current of Na-Ca exchnge in single ventricular cells of guinea-pig was studied under condition of constant $H^+$ with 10 mM BAPTA buffer, so the condition of intracellular $H^+$ may be different.

### The Effects of pH on Inward Current of Na-Ca Exchange

In the present study with single atrial cells of rabbit, the internal and external acidification reduced the inward current of Na-Ca exchange, while the internal and external alkalinization enhanced the Na-Ca exchange current. Other investigators reported that acidification reduced the Na-Ca exchange in the rod cell (Hodgkin and Nunn 1987), ventricular cells (Earm and Irisawa 1986), and cardiac sarcolemmal vesicles (Philipson *et al.* 1982), and that alkalinization enhanced the inward current of Na-Ca exchange in the rod cell and Na-Ca exchange in cardiac sarcolemmal vesicles but reduced the outward current of Na-Ca exchange in ventricular cell.

The Na-Ca exchange current can be activated by intracellular Ca transient released from SR in single atrial cells of rabbit (Earm *et al.* 1989). Thus change in pH could affect Na-Ca exchange current through the change in Ca current (Irisawa and Sato 1986; Yeum 1989). However, 1 $\mu$ M Bay K 8644 increased Ca current by 100 % and then increased Na-Ca exchange current by 20 % (Yeum 1989). The extent of decrease in Na-Ca exchange current by pH 6.0 (37 %) or increase in Na-Ca exchange current by pH 8.0 (34 %) are greater than that expected from the effect on Ca current, i.e. pH 5.5 decreased Ca current by 50 % (Irisawa and Sato 1986). In addition, assuming that acidic pH increases Ca uptake by SR (Nakamura and Schwartz 1972) and cause an increase of intracellular Ca via Na-Ca exchange following Na-H exchange (Kim and Smith 1988), the effects of pH on the Na-Ca exchange current is likely to be a direct one. Marked increase of the exchange current by an increased pH suggests the importance of histidine residue for the maximal activation (Wakabayashi and Goshima 1981) or the importance of protonation in two essential residues of the exchange molecule (Hodgkin and Nunn 1987).

The properties of Na-Ca exchange carrier, i.e. binding affinity to $Na_i$ or $Ca_i$ and $Na_0$ or $Ca_0$ (Kimura *et al.* unpublished data) and the position of energy barrier (Kimura *et al.* 1987; Earm *et al.* 1989), are not symmetric. Likely, the effects of pH on forward and reverse modes of Na-Ca exchange may not be symmetric based on our result with Na-free contracture and inward current of Na-Ca exchange in atrial myocytes of rabbit.

Although acidosis may increase intracellular Ca by inhibiting inward Na-Ca exchange current, the results presented here may be of special significance, especially in acidosis accompanying myocardial ischemia, considering the possible contribution of the Na-Ca exchange in cardiac excitation and contraction coupling and arrythmia (Hilgemann 1986; Hilgemann and Noble 1986).

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= 국문초록 =

## 토끼 심방근세포에서 pH가 Na-Ca 교환기전에 미치는 영향

서울대학교 의과대학 생리학교실

서인석 · 엄융의 · 김 전 · 황상익 · 호원경 · 김의용 · 안철수 · 박춘옥

pH가 Na-Ca 교환기전 중 reverse mode에 미치는 영향을 연구하기 위해 토끼 심방 trabeculae에서 Na-제거 경축의 변화를 관찰하고, forward mode에 미치는 영향을 연구하기 위해 단일 심방근세포에서 Na-Ca 교환 기전에 의한 내향 전류의 변화를 관찰하여 분석하였다.

심방 trabeculae를 적출하여 35°C에서 Na-제거 용액에 의해 유발된 Na-제거 경축을 기록 분석하였고, 단일 심방근세포는 collagenase/Langendorff 관류법을 이용하여 얻어서 whole-cell voltage clamp 방법으로 +40 mV, 2 ms 자극기간의 펄스 후 −70 mV에서 활성화되는 Na-Ca 교환기전에 의한 일과성 내향전류를 기록 분석하여 다음과 같은 결과를 얻었다.

1. 심방 trabeculae에서 세포외 pH를 낮추거나(수소이온농도의 증가) 높이거나 (수소이온농도의 감소) Na-제거 경축의 크기는 줄어들었다.
2. 심방 trabeculae에서 세포내 pH를 낮추거나 높이거나 Na-제거 경축의 크기는 증가하였다.
3. 단일 심방근세포에서 세포내외의 pH가 높아짐에따라 Na-Ca 교환전류의 크기가 증가하였다.
4. 단일 심방근세포에서 Na-H 교환기전을 억제하여 세포내 산성화를 유발하는 amiloride에 의해 Na-Ca 교환기전이 억제되었다.

이상의 결과로 보아 Na-Ca 교환기전에 미치는 pH의 영향은 reverse mode냐 forward mode냐에 따라 다른 것으로 사료된다.