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Involvement of a Na-Ca Exchange Mechanism in Contraction Induced by Low-Na Solution in Isolated Guinea-Pig Aorta

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Abstract. The possibility of involvement of a Na-Ca exchange mechanism in the contractile responses induced by a reduction of external Na concentration ($[Na]_0$) has been studied in isolated guinea-pig aorta. Low-Na (11.9 mM) solution (Li-substituted) produced a contraction in ouabain-treated muscles in the presence of phentolamine (10^{-6} M). The magnitude of the contraction was dependent on the duration of the pretreatment with ouabain (2×10^{-5} M). Ca-free solution, but not verapamil (10^{-6} M), abolished the contraction induced by low-Na solution. The muscles were loaded with various amounts of Na by incubating the tissue with ouabain and varying $[Na]_0$ (11.9–148.7 mM) in the absence of Ca. The magnitude of the contractions induced in these muscles by low-Na solution containing Ca (2.5 mM) was dependent on the cellular Na content. Loss of cellular Na into low-Na solution followed a single exponential time course and the rate coefficient of Na-loss in the presence of external Ca was about twice as great as in the absence of Ca. Cellular ^{45}Ca uptake in low-Na solution was significantly greater in Na-loaded tissues (pretreated with ouabain for 3 h) than in normal tissues. The ^{45}Ca uptake in low-Na solution was not inhibited by verapamil. These results suggest that the contraction induced by low-Na solution is caused by a Ca influx which is dependent on internal Na (a Na-Ca exchange mechanism).

Key words: Vascular smooth muscle – Na-Ca exchange mechanism – Low-Na solution – Cellular Na content – Cellular ^{45}Ca uptake

Introduction

In isolated smooth muscle preparations, reduction of external Na concentration ($[Na]_0$) is known to induce contraction (van Breemen et al. 1979). An attempt has been made to explain this contraction on the basis of a Na-Ca exchange mechanism (Reuter et al. 1973; Blaustein 1977). Other recent observations demonstrated that the contraction in rabbit aorta was inhibited by denervation or by α-adrenoceptor blockade (Karaki and Urakawa 1977). However, it has also been reported that the contraction induced by Na-free solution in rabbit ear artery was not blocked by phentolamine (Droogmans and Casteels 1979). The latter authors suggested that the contraction in the ear artery in Na-free medium was not attributable to a Na-Ca exchange mechanism.

In the previous reports, we demonstrated that ouabain and K-free solution produced increases in both tension and ^{45}Ca uptake in guinea-pig aorta in the presence of phentolamine, and suggested that these contractions were produced through a Na-Ca exchange mechanism (Ozaki et al. 1978; Ozaki and Urakawa 1979). Furthermore, we reported that rabbit arterial smooth muscles were less sensitive to the contractile effect of K-free solution and suggested that guinea-pig aorta is a better preparation to study the Na-Ca exchange mechanism (Ozaki and Urakawa 1980a). In the present study, we have therefore used the guinea-pig aorta and have investigated the changes in contractile responses, cellular Na content and cellular ^{45}Ca uptake in low-Na solution in order to obtain a better insight into the role of the Na-Ca exchange mechanism.

Materials and Methods

Preparations. Male guinea pigs (300–600 g) were killed by a blow on the neck and the thoracic aorta was removed. It was placed in physiological salt solution (PSS) and cleaned of surrounding connective tissue. For tension experiments, helical strips about 10 mm long and 3 mm wide were cut. For determination of tissue Na and ^{45}Ca content, vessels were cut open longitudinally and rectangular strips weighing 5–10 mg were prepared.

Solutions. Normal PSS contained (mM): NaCl 136.8, KCl 5.4, $CaCl_2$ 2.5, $MgCl_2$ 1.0, $NaHCO_3$ 11.9 and glucose 5.5. Ca-free solution was made by omitting $CaCl_2$ from the PSS without any substitution. In some experiments, EGTA (0.1 mM) was added to the Ca-free solution. Low-Na solution was prepared by replacing NaCl with isosmolar sucrose, choline-Cl (with atropine 10^{-6} M), LiCl or KCl. The high-K (45.4–65.4 mM) solution was made by adding appropriate amount of 2 M KCl stock solution to normal PSS to keep the $[Na]_0$ constant. The hyperosmolarity of the high-K solution (up to 70–80 mM) had little effect on the contractility of the vascular smooth muscle. All solutions contained phentolamine (5×10^{-7}–10^{-6} M) in order to eliminate any effects due to neuronal release of catecholamine. Solutions were aerated with 95% O_2–5% CO_2 mixture and used at 37°C and pH 7.2.

Measurement of Tension. The muscle strips were suspended in an organ bath (20 ml) and contractions were recorded isometrically with a strain-gauge transducer (Nihon-Kohden). The resting tension applied to the muscle strips was 1 g. The muscles were allowed to equilibrate in normal PSS for at least 3 h until the response to high-K solution became stable. The magnitude of contraction induced by high-K (65.4 mM), which was 1.02 ± 0.07 g ($n = 18$), was used as a reference response (100%).

Change in Cellular Na Content. Cellular Na content was measured by the "Li-method" which was developed by Friedman (1974) for the rat tail artery. After incubation with test solution, the muscles were exposed to Li-solution (LiCl 147.4 mM, glucose 5.5 mM and Tris-HCl 11.9 mM) at 1°C and pH 7.2 for 15 min in order to remove extracellular Na. The tissues were then heated at 180°C in 0.5 ml of a mixture containing equal amounts of HNO_3 (61%) and $HClO_4$ (60%). Immediately before determination, the dried samples were dissolved in 0.01 N HCl. CsCl

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(1000 ppm) was added to the standard and to the diluted solutions in order to inhibit mutual interference of Na and K. Na concentration of the diluted samples was measured using flame photometer (Hitachi, Type 208, Japan).

Change in Cellular ^{45}Ca Content. ^{45}Ca uptake was measured by the modified "La-method" which was developed by Karaki and Weiss (1979) for rabbit aorta. After incubation with various test solutions labelled with ^{45}Ca (1 μCi/ml, New England Nuclear, USA), the muscles were exposed to a high-La solution ($LaCl_3$ 73.8 mM, glucose 5.5 mM and Tris-HCl 11.9 mM) at 1°C and pH 7.2 for 1 h in order to remove extracellular bound ^{45}Ca. The muscles were then placed in scintillation vials containing 0.5 ml of tissue solubilizer (Soluene-350, Packard Instr., USA) and were digested overnight at 50–60°C. The solubilized samples were then mixed with 5 ml of scintillator (Insta-Gel, Packard Instr., USA) and radioactivity was determined using liquid scintillation spectrometer (Tri-Carb, 3380, Packard, USA).

Drugs. Drugs used were ouabain (Merck, Darmstadt, FRG), verapamil (Eisai, Tokyo, Japan), phentolamine methylate (Ciba-Geigy, Basel, Switzerland) and atropine sulphate (Tokyo-Kasei, Tokyo, Japan).

Results

Contraction of Normal Tissue in Low-Na Solution

Exposure of the guinea-pig aorta to low-Na (11.9 mM) solution induced contractions. The magnitude and the time course of the contractions depended on the Na substitutes used. Sucrose-solution produced a phasic contraction followed by a sustained one (Fig. 1 A). Choline-solution also produced a sustained contraction but the rate of rise was slower than that of the contraction induced by sucrose-solution (Fig. 1 B). In Li-solution, the change in basal tone was very small (Fig. 1 C). The contraction induced by sucrose-solution was unaffected by verapamil (10^{-6} M), but this drug partially inhibited the contraction induced by choline-solution. Since the contraction induced by Li-solution was very small, the effect of verapamil on this contraction was not apparent.

Contraction in Na-Loaded Tissue in Low-Na Solution

Figure 1 also shows that, after incubation of the muscle strips with ouabain (2×10^{-5} M) for 30 min, lowering the $[Na]_o$ to 11.9 mM caused more rapid and larger contractions than those in normal tissues. It has been reported that this concentration of ouabain produces a maximum inhibition of the Na-K pump in guinea-pig aorta (Ozaki and Urakawa 1980b). The contractions observed in sucrose- and choline-solutions were sustained. On the other hand, when Li was used as a Na substitute, the contraction reached maximum after about 15 min followed by a gradual decrease in tension. Figure 1 D demonstrates that K-substituted solution produced a contraction similar to that induced by Li-solution when Ca channels are blocked by verapamil (10^{-6} M).

The magnitude of the contraction induced by a low-Na solution depended on the duration of the preincubation with ouabain (Fig. 2). When the preincubation period was longer than 40 min, ouabain itself induced a delayed tonic contraction by an accumulation of Na as described before (Ozaki et al. 1978; Ozaki and Urakawa 1979). If the incubation period with ouabain was kept constant at 30 min, and then the muscles were contracted by differing $[Na]_o$ solutions, the magnitude of the contraction induced by low-Na (11.9–103.1 mM) solution increased as the $[Na]_o$ decreased (Fig. 3).

The contractions of ouabain-treated aorta induced by sucrose-, choline- and Li-solutions were unaffected by vera-

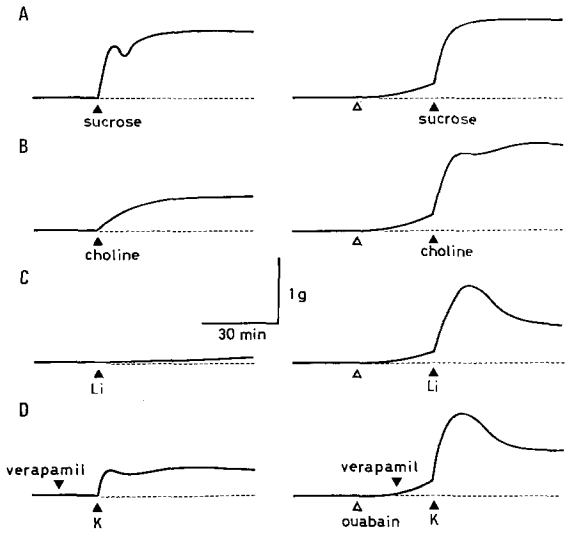

Fig. 1A–D. Tension development in normal tissue (*left*) and Na-loaded tissue (*right*) on exposure to low-Na (11.9 mM) solution. Na-loaded tissues were prepared by treating the muscles with ouabain (2×10^{-5} M) for 30 min before the application of low-Na solution. Four different Na substitutes were used; sucrose (**A**), choline (**B**), Li (**C**) and K (**D**). Muscles were pretreated with verapamil (10^{-6} M) before they were soaked in K-substituted solution in order to inhibit the voltage sensitive Ca channels

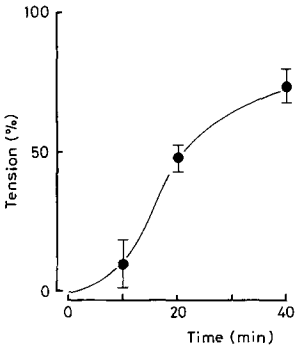

Fig. 2. Relationship between low-Na-induced contraction and duration of pretreatment with ouabain (2×10^{-5} M). The muscles were pretreated with oabain for 10, 20 and 40 min before they were exposed to low-Na (11.9 mM) solution (Li-substituted). *Ordinate:* relative contraction (%). *Abscissa:* time (min). Given are the mean values ± S.E. of 4 experiments. Muscle contraction induced by 65.4 mM KCl was used as reference (100%)

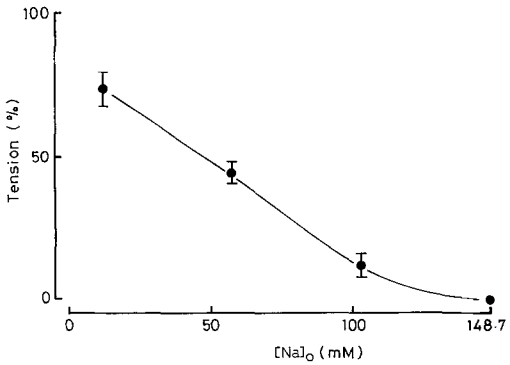

Fig. 3. Changes in tension in varying external Na concentrations. The muscle strips were pretreated with ouabain (2×10^{-5} M) for 30 min before they were exposed to varying low-Na concentrations (Li-substituted). *Ordinate:* tension (%). *Abscissa:* external Na concentration (mM). Given are the mean values ± S.E. of 5–8 experiments

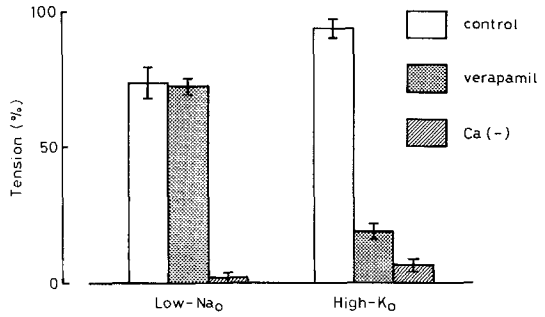

Fig. 4. Effects of verapamil and Ca-depletion on the contractions induced by low-Na (11.9 mM) solution (Li-substituted) in Na-loaded tissue and by high-K (45.4 mM) solution in normal tissue. The muscles were pretreated with verapamil (10^{-6} M) for 10 min or with Ca-free solution (EGTA 0.1 mM) for 15 min before they were contracted by low-Na or high-K solution. Na-loaded tissue was made by pretreating with ouabain (2×10^{-5} M) for 40 min. Given are the mean values ± S.E. of 4–6 experiments

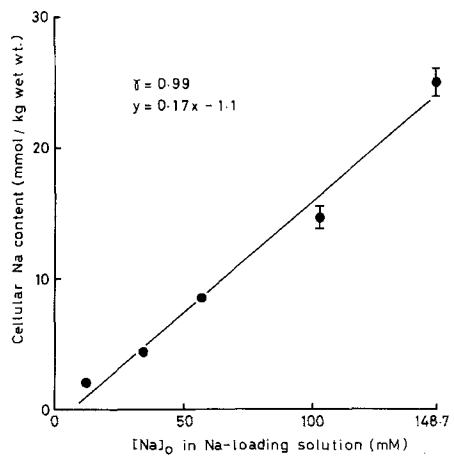

Fig. 5. Relationship between cellular Na content and $[Na]_0$ in Na-loading solution. Muscles were pretreated with Ca-free, Na-loading solution containing different $[Na]_0$ (Li-substituted) and ouabain (2×10^{-5} M) for 3 h. After the Na-loading, the muscles were washed 15 min with cold Li-solution for the measurement of cellular fraction of Na. Cellular Na increases linearly with raising $[Na]_0$ in Na-loading solution ($\gamma = 0.99$). *Ordinate:* $[Na]_0$ in Na-loading solution. *Abscissa:* cellular Na content (mmol/kg wet weight). Given are the mean values ± S.E. of 6 experiments

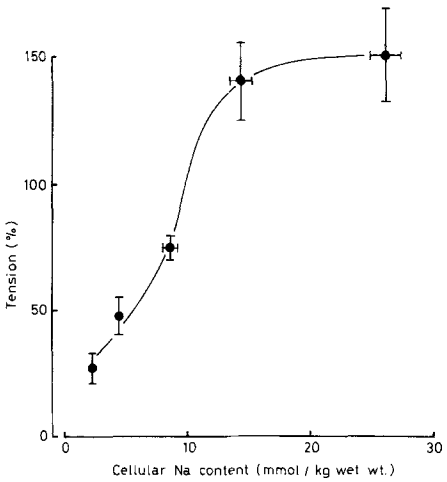

Fig. 6. Relationship between cellular Na content and tension development. Muscles were incubated for 3 h in the Ca-free, Na-loading solution containing different $[Na]_0$, as shown in Fig. 5. They were then contracted by low-Na (11.9 mM) solution (Li-substituted) containing Ca (2.5 mM). *Ordinate:* tension (%) ($n = 4-8$). *Abscissa:* cellular Na content (mmol/kg wet weight) adopted from Fig. 5

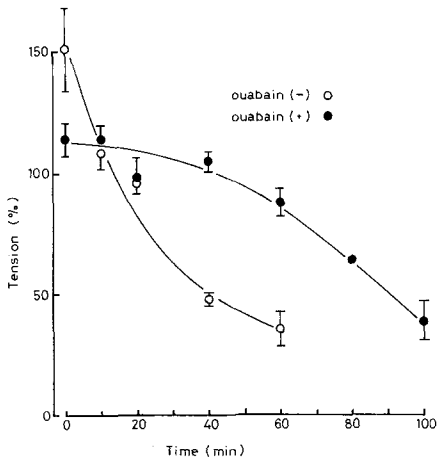

Fig. 7. Contractions of Na-loaded muscle induced by adding Ca during incubation in low-Na solution. Muscles were loaded with Na in Ca-free solution containing ouabain (2×10^{-5} M) for 3 h. They were then transferred to Ca-free, low-Na (11.9 mM) solution (Li-substituted) with (●) or without (○) ouabain to washout cellular Na. After a desired wash period, the muscles were contracted by adding Ca (2.5 mM) to the Na-wash solution. *Ordinate:* tension (%). *Abscissa:* wash period (min). Given are the mean values ± S.E. of 4–8 experiments

pamil (10^{-6} M). The contraction induced by sucrose-solution persisted for more than 30 min after the removal of external Ca and the addition of EGTA 0.1 mM, while Ca-depletion did inhibit the contractions induced by choline- and Li-solutions. Addition of verapamil (10^{-6} M) or removal of external Ca strongly inhibited the contraction induced by high-K (45.4 mM) solution (Fig. 4).

Relationship Between Tension and Cellular Na

Cellular Na content was changed by two different procedures. In the first procedure, tissues were incubated for 3 h in various Ca-free, Na-loading solution ($[Na]_0$: 11.9–148.7 mM, Li-substituted) all of which contained ouabain (2×10^{-5} M). As shown in Fig. 5, cellular Na content measured with "Li-method" (Friedman 1974) was higher when the $[Na]_0$ in the Na-loading solution was higher, and a linear relationship was obtained between these parameters ($\gamma = 0.99$, $P < 0.01$). After the Na-loading, the muscles were transferred to a low-Na (11.9 mM) solution (Li-substituted) containing Ca (2.5 mM). The magnitude of the muscle contraction induced in the low-Na solution was dependent on the $[Na]_0$ in the Na-loading solution and, therefore, on the cellular Na content. The relationship between muscle tension and cellular Na content is shown in Fig. 6.

In the second procedure used to change the cellular Na content, tissues previously loaded with Na by incubating 3 h with a Ca-free solution containing ouabain, were transferred

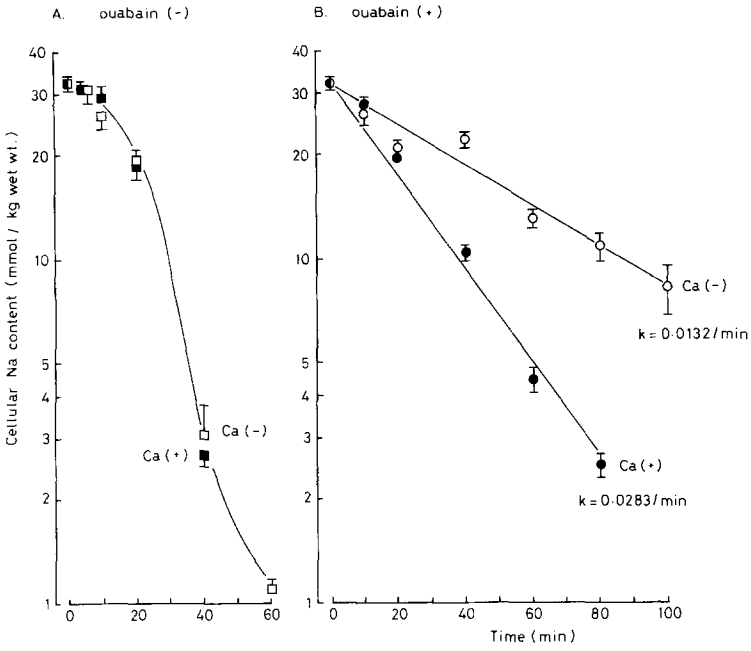

Fig. 8A and B
Loss of cellular Na from Na-loaded aorta during washout with low-Na solution. Tissues were preincubated in Ca-free solution containing ouabain (2×10^{-5} M) for 3 h prior to washout with low-Na (11.9 mM) solution (Li-substituted) in the absence (**A**) or presence (**B**) of ouabain and in the presence (■, ●) or absence (□, ○) of external Ca (2.5 mM). In low-Na solution containing ouabain, the rate of Na loss exhibited single exponential curves. *Ordinate:* cellular Na content (mmol/kg wet weight). *Abscissa:* time (min). Given are the mean values ± S.E. of 6–8 experiments

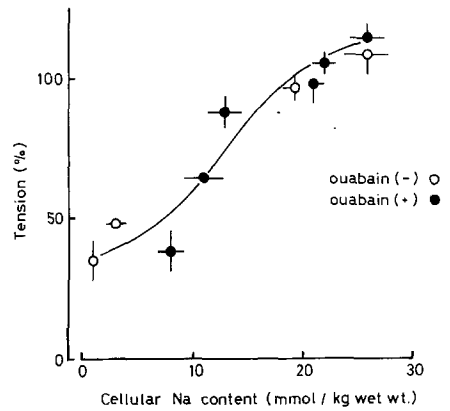

Fig. 9. Relationship between tension development and cellular Na content. Values are adopted from Fig. 7 and 8. (●); low-Na solution with ouabain. (○); low-Na solution without ouabain. *Ordinate:* tension (%). *Abscissa:* cellular Na content (mmol/kg wet weight)

to Ca-free, low-Na solution with or without ouabain to wash out a part of the cellular Na. After the desired wash period, the muscles were contracted by adding Ca (2.5 mM) to the Na-wash solution. The magnitude of the contraction was less when the duration of Na wash period was longer (Fig. 7). It was also found that the rate of decay of the contraction was much faster in the Na-wash solution without ouabain than in the solution which contained ouabain. In accordance with the tension experiments, the rate of loss of Na into low-Na solution was much faster in the absence of ouabain than in the presence of this agent (Fig. 8). Since Li can substitute for K in activating the Na-K pump, cellular Na might exchange more rapidly through an ouabain-sensitive Na-K pump in the absence of ouabain. As shown in Fig. 9, the relationship between cellular Na and the tension development obtained in these experiments is similar to that obtained in the experiments shown in Fig. 6.

In the next experiment, the effect of extracellular Ca on the loss of cellular Na was investigated. The loss of Na into a low-Na solution without ouabain from a Na-loaded aorta (pretreated with ouabain for 3 h) did not exhibit a single exponential time course and there was no significant difference between the rates of Na-loss in the presence and absence of Ca (2.5 mM) (Fig. 8A). On the other hand, the loss of Na into a low-Na solution which did contain ouabain was faster in the presence of Ca; in these cases the rates of loss could be described by a single exponential with a rate constant of 0.0283 ± 0.0029/min ($T_{1/2}$ = 24.5 min) in the presence or 0.0132 ± 0.0012/min ($T_{1/2}$ = 52.7 min) in the absence of Ca (Fig. 8).

Change in Cellular ^{45}Ca Content in Low-Na and High-K Solutions

The change in cellular ^{45}Ca content was measured by a modified "La-method" (Karaki and Weiss 1979). The resting $^{45}Ca-^{40}Ca$ exchange of normal tissue in normal PSS had reached a plateau level within 20 min (267.9 ± 26.9 µmol/kg wet weight, $n = 6$). Therefore, the ^{45}Ca uptake in labelled low-Na and in high-K solutions was examined over 20 min periods. As shown in Fig. 10, uptake of ^{45}Ca in low-Na, Li-solution was significantly greater in Na-loaded tissue (pretreated with ouabain for 3 h) than in normal tissue. A large increase in ^{45}Ca uptake by Na-loaded tissue was also observed in choline-substituted solution; 857.4 ± 79.8 ($n = 6$) in Na-loaded tissue and 481.0 ± 52.1 µmol/kg wet weight ($n = 6$) in normal tissue. High-K (65.4 mM) solution also increased the ^{45}Ca uptake. Figure 10 illustrates the effect of verapamil on ^{45}Ca uptake induced by low-Na and high-K solutions. While verapamil (10^{-6} M) scarcely affected the increased ^{45}Ca uptake in low-Na solution, it significantly inhibited the K-stimulated ^{45}Ca uptake.

Discussion

It is apparent from the present experiments that exposure of guinea-pig aorta to low-Na solution induces a contraction. When sucrose was used as a Na substitute, the low-Na solution produced a large contraction which was not dependent on external Ca. Casteels and Raeymaekers (1977)

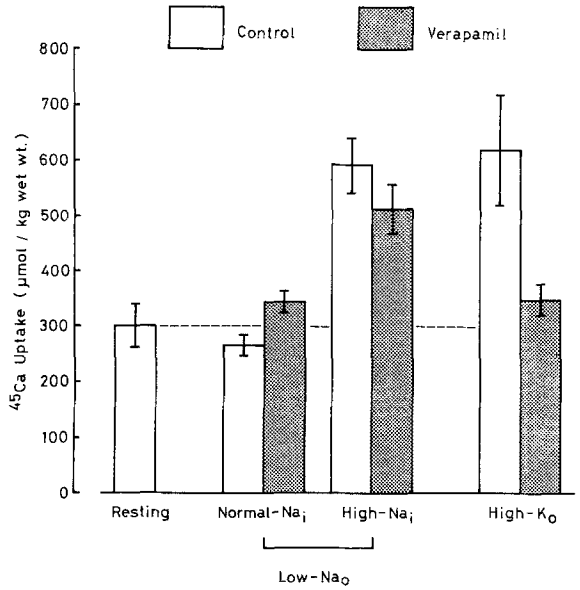

Fig. 10. ^{45}Ca uptake for 20 min in low-Na (11.9 mM) solution (Li-substituted) or high-K (65.4 mM) solution. Na-loaded tissues were prepared by treating the muscles with ouabain (2×10^{-5} M) for 3 h. Some tissues were pretreated with verapamil (10^{-6} M) for 10 min before they were exposed to radioactive low-Na or high-K solution. Low-Na solution increased ^{45}Ca uptake in Na-loaded tissues but not in normal tissues. Note that verapamil had no effect on the increase in ^{45}Ca uptake induced by low-Na solution, while the agent significantly ($P < 0.05$) inhibited the K-stimulated ^{45}Ca uptake. Given are the mean values ± S.E. of 6–8 experiments

have pointed out that sucrose-solution exerts osmotic effects because of the low membrane permeability. It must also be taken into account that the sucrose-solution is deficient in Cl and that the ionic strength of the solution is low. In the case of Na-free, choline-substitution, it has been reported that such a solution depolarizes the cells of rabbit ear artery by about 10 mV (Droogmans and Casteels 1979). Certainly such membrane depolarization might be involved in the contraction induced by choline-solution in guinea-pig aorta, for verapamil (an inhibitor of Ca channels) partially inhibited the contraction. Thus a part of the contraction induced by sucrose- or choline-solution might be attributable to the direct effect of the Na substiutes rather than to the effect of reduced $[Na]_0$. In this study, therefore, we have also used Li as a Na substitute. In the Li-solution, Na-loading effects were even more obvious than in sucrose- or choline-solution. Our results also demonstrated that (providing Ca channels were blocked by verapamil) K, when used as a Na substitute, produced similar effect to Li.

Removal of external Na produced more rapid and greater contraction in tissues previously loaded with Na than in normal tissues. The contractile tension increased with an increase in cellular Na and a concomitant increase in ^{45}Ca uptake was also apparent. Furthermore, loss of Na into low-Na solution was reduced in the absence of external Ca. These results suggest that lowering $[Na]_0$ augments a loss of Na from the cell which is coupled with Ca influx by means of Na-Ca exchange carrier, this in turn causing contraction in guinea-pig aorta.

When muscles were exposed to low-Na, Li-solution, there was only a small change in tension in normal tissues. Even in Na-loaded tissues, the contraction was transient and returned to the original level after prolonged incubation in low-Na, Li-solution. Furthermore, the low-Na solution increased ^{45}Ca uptake only in Na-loaded tissues and not in normal tissues. Van Breemen (1975) also observed that there was only a small increase of ^{45}Ca uptake by rabbit aorta in Na-free, Li-solution. Furthermore, Na-free solution increased ^{45}Ca uptake of the guinea-pig taenia coli but only when the tissue was Na-loaded (Brading and Widdicombe 1975; Brading 1978). These data suggest that, even in the absence of transmembrane Na gradient, Ca can be removed from the cell. Therefore, it is not likely that a Na-Ca exchange mechanism is the sole mechanism for Ca extrusion; some other Ca extruding processes must also operate in this tissue.

Verapamil inhibited the contraction induced by high-K but not by low-Na solution. Verapamil also inhibited the K-stimulated ^{45}Ca uptake but had little effect on the low-Na-stimulated ^{45}Ca uptake. It is known that organic "Ca antagonists", such as verapamil and nifedipine, specifically inhibit a Ca channel in many types of cells (Fleckenstein 1977). In vascular smooth muscles, the Ca influx triggered by high-K or other depolarizing agent (TEA) (Droogmans et al. 1977; Haeusler et al. 1980) is markedly inhibited by these "antagonists". Thus, these data suggest that the contraction induced by low-Na solution in guinea-pig aorta is initiated by a mechanism which is different from that of depolarization-induced contraction. It has been reported that in squid axon the "Ca antagonist" does not affect carrier mediated Na-Ca exchange (Baker 1978). It has also been reported that in cardiac muscle verapamil and D600 have little effect on the contraction induced by low-Na solution, although they inhibit the twitch contraction and K-induced contraction (Chapmann and Ellis 1978).

In conclusion, we have demonstrated a fraction of Ca influx which is dependent on intracellular Na, and a fraction of Na efflux which is dependent on extracellular Ca. These results support the existence of a Na-Ca exchange in guinea-pig aorta.

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