Effects of Ouabain and Low Sodium on Contractility of Human Resistance Arteries

Robin G. Woolfson, Philip J. Hilton, and Lucilla Poston

Earlier work with rat arteries has resulted in a widely held assumption that resistance artery smooth muscle will not contract on exposure to a reduced transplasmalemmal sodium gradient. In view of the well-recognized low sensitivity of rat tissue to cardiac glycosides, we have investigated the effects of altering the transplasmalemmal sodium gradient on vascular smooth muscle tone by using human resistance arteries. Incubation of arteries in low sodium or in ouabain to inhibit active sodium efflux for 1 hour increased the contractile response to caffeine stimulation; this finding indicated enhanced calcium buffering by the sarcoplasmic reticulum. Prolonged incubation in ouabain in the presence of phentolamine or diltiazem resulted in a concentration-dependent increase in the tone of resting human resistance arteries. Reduction of the transplasmalemmal sodium gradient by incubation in low sodium buffer effected an increase in tone similar to that obtained in the presence of ouabain. These results suggest that alteration of the transplasmalemmal sodium gradient may increase the vascular smooth muscle tone of human resistance arteries by altering intracellular calcium handling. This is a new finding in human resistance arteries and may involve inhibition and, indeed, reversal of sodium-dependent calcium efflux. A concentration-dependent potentiation of tone was found after the addition of ouabain to submaximally activated arteries. Sodium-calcium exchange may also play a pivotal role in this mechanism. (Hypertension 1990;15:583–590)

Since the original observation by Tobian and Binion, who demonstrated raised sodium content in the arteries of patients with essential hypertension, considerable evidence has accrued from other cell types that suggests a generalized defect of sodium transport in essential hypertension. The most consistent data has come from studies of peripheral blood leucocytes and supports the view that the raised intracellular sodium is the consequence of serum-induced inhibition of the sodium pump, sodium-potassium adenosine triphosphatase (Na-K-ATPase). However, there is increasing evidence that the sodium-hydrogen (Na-H) antiporter may also be involved. This was originally suggested by the work of Canessa et al, who documented abnormally high sodium-lithium (Na-Li) exchange in essential hypertension. Because the Na-Li exchanger may also transport sodium ions for hydrogen ions, a net increase of intracellular sodium might result. More recently, however, there have been a number of reports of patients with essential hypertension displaying abnormally high activity of the Na-H antiporter itself.

There is some controversy as to whether the elevation of intracellular sodium in vascular smooth muscle may have an etiological role in the development of increased peripheral resistance associated with essential hypertension. In large arteries, there is good evidence that raised intracellular sodium is associated with myogenic contraction. By use of cardiac glycosides for elevation of intracellular sodium, myogenic vasoconstriction has been shown to develop in rabbit aortic strips and rat aortic rings, rat and guinea pig aortic rings, and human crural and omental vessels. Blaustein and colleagues have postulated that these effects may be mediated by inhibition of sodium-dependent calcium efflux. They have hypothesized that sodium-calcium (Na-Ca) exchange activity is controlled by the transplasmalemmal sodium gradient and that a reduced gradient inhibits and perhaps reverses Na-Ca exchange; this occurrence results in accumulation of intracellular calcium and stimulation of the contractile process. This is supported by the semiquantitative observations of increases in the size of the noradrenaline and caffeine-sensitive intracellular calcium stores in rat aortic rings exposed to ouabain in...
the presence of diltiazem or nitrendipine. More recently, using calcium-sensitive fluorescent dyes, Nabel et al have demonstrated an inverse relation between extracellular sodium and intracellular calcium concentrations in rat vascular smooth muscle cells. This relation was shown to be independent of potential-dependent calcium influx and thus provided indisputable evidence for the presence of a Na-Ca exchange mechanism.

In smaller arteries the relation between transplasmalemmal sodium gradient, intracellular calcium, and vascular tone is less clear. It is, of course, these vessels that make the greatest contribution to peripheral vascular resistance. In contrast to the work in large arteries, Mulvany and colleagues have shown that a reduced transplasmalemmal sodium gradient has no effect on tension in resistance vessels. This experimental situation was produced either by incubation of resting rat mesenteric arteries in low sodium buffer or by incubation of rat and guinea pig femoral and mesenteric arteries in ouabain (a specific Na, K-ATPase inhibitor). Consequently, it has generally been assumed that Na-Ca exchange is an unimportant process in resistance arteries. Furthermore, this data has argued against a causal role for raised intracellular sodium in the increased peripheral vascular resistance found in hypertension.

In this study of human resistance arteries, our aims were twofold: first, to investigate the influence on tone of raised intracellular sodium produced by Na, K-ATPase inhibition and second, to investigate a possible role of Na-Ca exchange in these arteries in the control of tone.

Methods

Human subcutaneous resistance arteries (n=92) with a mean internal diameter of 213±7 μm were obtained from biopsies of anterior abdominal wall fat taken during routine abdominal surgery on 55 normotensive patients who were receiving no medication (40 women; mean age, 47±2 years; mean blood pressure, 131±2/79±1 mm Hg). The arteries were dissected free from connective tissue and were mounted as a ring preparation on a myograph capable of measuring isometric tension. The arteries were bathed in physiologic salt solution (PSS) at a pH of 7.4 at 37° C and bubbled with 5% CO2 in O2. The vessels were equilibrated in PSS for 1 hour, and the passive tension–internal circumference characteristics of the arteries were then determined. The arteries were stretched to achieve an internal circumference equivalent to 90% of that which they would have had when relaxed in situ under a transmural pressure of 100 mm Hg (the maximum active tension for the minimum resting tension is developed at approximately this circumference). To assess their contractile response, the arteries were then maximally contracted for 2 minutes every 10 minutes on five occasions. The first, second, and fifth contractions were produced with 5 μM norepinephrine in 125 mM potassium solution; the third contraction was produced with 5 μM norepinephrine in PSS, and the fourth contraction was produced with 125 mM potassium solution. Any artery failing to produce a maximum active tension equivalent to a pressure of 100 mm Hg was rejected. The fifth contraction was taken as the maximal contraction (see later). Tension was measured in millinewtons per millimeter length of vessel.

Cumulative Dose-Response Relation of Resting Human Resistance Arteries to Ouabain

To investigate the effect of increasing concentrations of ouabain, a cumulative dose-response study was performed. Resting resistance arteries were incubated in ouabain (0.1 μM, 1 μM, and 10 μM) for 2 hours sequentially at each concentration. Change in tension was recorded at 15-minute intervals throughout the 6-hour duration of each experiment. The bathing solution was replaced every 15 minutes. Arteries were incubated in PSS for 6 hours as timed control.

Prolonged Incubation of Resting Arteries in Different Concentrations of Ouabain

To investigate whether ouabain-induced increased tension of resting resistance arteries might be a time-dependent phenomenon, arteries were incubated in 10 nM or 10 μM ouabain for 6 hours. Changes in tension were recorded at 30-minute intervals. The bathing solution was replaced every 15 minutes.

Prolonged Incubation of Arteries in Ouabain and Phentolamine or Diltiazem

To investigate whether ouabain-induced increased tension of resting resistance arteries might be due to an action of ouabain on the neuromuscular junction or to depolarization, resting resistance arteries were incubated for 6 hours in 10 μM ouabain in the presence of either 1 μM phentolamine or 1.6 μM diltiazem for 6 hours. Changes in tension were recorded at 30-minute intervals. The bathing solution was replaced every 15 minutes.

Comparison of Prolonged Incubation of Arteries in Ouabain With Prolonged Incubation in Low Sodium Buffer

The transplasmalemmal sodium gradient may be reduced either by increasing intracellular sodium (e.g., with ouabain) or by reducing extracellular sodium. In this experiment, arteries were incubated in low sodium buffer [equimolar substitution of choline chloride for sodium chloride in PSS; sodium concentration ([Na]) 25 mM] for 6 hours. Tension was recorded at 30-minute intervals. The bathing solution was replaced every 15 minutes. At the end of the incubation, the arteries were washed in PSS and observed for a further 5 minutes.
Resistance Arteries
Incubation in Low Sodium Buffer on the Effect of Incubation of Arteries in Ouabain and of

To investigate the short-term effects of a reduced transplasmalemmal sodium gradient on calcium handling by resting human resistance arteries, we examined the effects of ouabain and low sodium on the relative size of the intracellular caffeine-sensitive calcium stores in the sarcoplasmic reticulum. Caffeine discharges calcium from caffeine-sensitive stores in the sarcoplasmic reticulum^24; this occurrence results in a transient increase in vascular tension. The arteries were exposed to 10 mM caffeine in calcium-free PSS for 30 seconds, and the peak change in tension was recorded. The arteries were washed vigorously with PSS ([Ca^2+] concentration (ICa^2+)) 2.5 mM) 12 times and were rested for 10 minutes, after which the caffeine stimulation followed by washing was repeated. The arteries were then incubated for 1 hour (and thereafter) in 10 μM ouabain or in low sodium buffer (25 mM) or in PSS as control. Then caffeine stimulation was performed twice more as already described.

Effect of Ouabain on Precontracted Resistance Arteries

Norepinephrine concentration–response curves (from 0.02 to 10 μM) were constructed for the arteries used, and the concentration producing about 50% of maximum contraction was calculated. The arteries were then submaximally contracted with this concentration of norepinephrine in the presence of 3 μM cocaine (to exclude the possibility that any effect of ouabain was due to inhibition of presynaptic uptake of norepinephrine^25). The initial contraction reached a plateau after 4 minutes, and subsequent changes in tension were recorded every 4 minutes for a further 32 minutes. The experiment was then repeated, but on this occasion, after 4 minutes the arteries were sequentially exposed to 1 nM, 11 nM, 0.111 μM, and 10.1 μM ouabain for 4 minutes at each concentration. The arteries were incubated with the final concentration of ouabain (10.1 μM) for a further 16 minutes. Again, changes in tension were recorded at 4-minute intervals, as within that time the potentiating effect of ouabain had plateaued.

To exclude the possibility that the effect was mediated by ouabain-induced neural release of norepinephrine,^26,27 we performed similar experiments using potassium solution to submaximally precontract arteries in the presence of 10 μM phenolamine. The concentration of potassium solution was calculated by first constructing potassium concentration–response curves for each artery and by using the concentration producing about 50% of maximal contraction (range of K^+ concentration, 18–30 mM). In these experiments, the arteries were contracted for 16 minutes in total. After control procedures had been performed, the arteries were sequentially exposed to 1 nM, 0.11 μM, and 10.1 μM ouabain for 4 minutes at each concentration. As before, changes in tension were recorded at 4-minute intervals after a 4-minute stabilization of the initial contraction.

Chemicals

Choline chloride (British Drug House Chemicals Ltd, Poole, UK), ouabain (British Drug House Chemicals Ltd), norepinephrine (Winthrop, Guildford, UK), caffeine (Sigma Chemical Co., St. Louis, Missouri), and phenolamine (CIBA, Horsham, UK) were used in the studies. The arteries were bathed in PSS containing (mM) NaCl 119, CaCl2 2.5, MgSO4 1.17, NaHCO3 25, KH2PO4 1.18, EDTA 0.026, and glucose 5.5, pH 7.4, at 37° C, bubbled with 5% CO2 in O2. Maximal potassium activation was achieved by using PSS with an equimolar substitution of KCl for NaCl, which resulted in a final K^+ concentration of 125 mM.

Arteries were used for only one experiment involving ouabain as the effects were irreversible.

Statistical Analysis

Values are expressed as mean±SEM. Differences between means were assessed by two-tailed paired or unpaired t tests as indicated. Analysis of variance was used to assess p in the caffeine experiments. To measure association between data, Spearman's rank correlation coefficient (RS) was calculated for n paired observations, and a two-tailed p value was given. The criterion for statistical significance was taken as p<0.05.

Results

Cumulative Dose-Response Relation of Resting Human Resistance Arteries to Ouabain

At the lowest concentration of ouabain (0.1 μM), no significant change in tension occurred after 2 hours (0.01±0.03 mN/mm [n = 7 arteries] vs. 0.07±0.04 mN/mm [n = 6 arteries]). However, during the incubation in 1 μM ouabain, the tension rose progressively with time (RS, 0.929; p<0.001; n = 8 points) and had become significantly greater than that of the control incubation after 1 hour (0.05±0.05 mN/mm [n = 7 arteries] vs. 0.09±0.04 mN/mm [n = 6 arteries]; p<0.05). At the end of 2 hours of incubation in 1 μM ouabain, tension was 0.08±0.06 mN/mm (n = 7 arteries) compared with −0.13±0.06 mN/mm (n = 6 arteries) for control incubation (p<0.025). The tension continued to rise progressively during the incubation in 10 μM ouabain (RS, 0.976; p<0.001; n = 8 points) and at the end of 2 hours was 0.57±0.19 mN/mm (n = 7 arteries) compared with −0.13±0.04 mN/mm (n = 6 arteries) for control incubation (p<0.001) (Figure 1).

Comparison Between Prolonged Incubation in 10 nM and 10 μM Ouabain and Control Incubation

The final mean tension achieved at 6 hours was greater in those arteries exposed to 10 μM than to 10 nM ouabain (0.81±0.20 mN/mm [n = 7 arteries] vs.
Hypertension Vol 15, No 6, Part 1, June 1990

0.26±0.05 mN/mm [n=6 arteries], respectively; p<0.04). Tension rose progressively in both groups (RS=0.958, p<0.001, and n=12 points for the 10 μM ouabain group; RS=1.000, p<0.001, and n=12 points for the 10 nM ouabain group). The final tensions in each group were significantly greater than in the control group (−0.13±0.04 mN/mm [n=6 arteries]) at 6 hours (p<0.005 for the 10 μM ouabain group; p<0.001 for the 10 nM ouabain group). See Figure 2 for comparisons among the three groups. The final mean tension achieved by arteries incubated in 10 μM ouabain was 29% of their mean maximal tension as compared with 7% for arteries incubated in 10 nM ouabain (see Methods). The data for the control group were the same as those used in the previous experiment.

Comparison Between Prolonged Incubation in 10 μM Ouabain Alone and Ouabain With 1 μM Phentolamine or 1.6 μM Diltiazem

The six arteries incubated in ouabain and phentolamine demonstrated a progressive rise in mean tension similar to that in the seven arteries incubated in ouabain alone. Final mean tension was not significantly different (0.52±0.17 mN/mm for the phentolamine group [n=6] vs. 0.81±0.20 mN/mm for ouabain alone [n=7]; p=NS). However, in the presence of diltiazem, the final tension was reduced (0.32±0.05 mN/mm for the diltiazem group [n=6] vs. 0.81±0.20 mN/mm for ouabain alone [n=7]; p<0.05). See Figure 3 for group comparisons. The data for the control and 10 μM ouabain groups were the same as those used in the previous experiment.

Prolonged Incubation of Arteries in Low Sodium Buffer

Tension rose progressively throughout the 6 hours of incubation in low sodium (RS=0.979, p<0.001, and n=12 points). At the end of the incubation, the tension was significantly different from the timed control (1.01±0.42 mN/mm for the low sodium group [n=7 arteries] vs. −0.13±0.04 mN/mm for the control group [n=6 arteries]; p<0.05). There was no statistically significant difference between mean tensions of the seven arteries incubated in low sodium or of the seven arteries incubated in 10 μM ouabain (Figure 4). The final mean tension achieved by the arteries incubated in low sodium was 39% of their
mean maximal tension. The increased tension in the low sodium medium was rapidly reversed after washing in isotonic PSS (within 5 minutes), whereas the increased tension in the ouabain group appeared to be irreversibly raised. The data for the control and 10 µM ouabain groups were the same as those used in the previous experiment.

Effect of Incubation of Arteries in Ouabain and in Low Sodium Buffer on Caffeine-Sensitive Calcium Store

Exposure to caffeine produced a transient rise in tension in all arteries (0.66±0.06 mN/mm; n=28), which correlated with the diameters of the artery (RS=0.688; n=28; p<0.001). The second exposure to caffeine produced 0.64±0.06 mN/mm (p=NS when compared with the first exposure). Given this and the range of artery diameters (111-333 µm), the tensions produced by exposure to caffeine are expressed as relative tensions (calculated by dividing the tensions produced by each caffeine stimulation by the tension produced by the first caffeine stimulation). Between the second and third caffeine exposures, arteries were incubated for 1 hour in 10 µM ouabain (n=10), low sodium (n=8), or PSS (n=10). One hour of incubation with ouabain increased the caffeine-induced relative tension (from 0.97±0.04 to 1.15±0.07; n=10; p<0.01). Similarly, 1 hour of low sodium incubation increased the relative tension response (from 1.02±0.03 to 1.09±0.05; n=8; p<0.01). These responses were not significantly different from each other, and neither response changed significantly on the subsequent (fourth) caffeine exposure. One hour of incubation in PSS alone slightly reduced the relative tension response (from 0.94±0.05 to 0.88±0.07; n=10, p=NS), and there was also no significant difference in relative tensions between the third and fourth exposures. Figure 5, top panel, shows a representative tracing; Figure 5, bottom panel, shows the relative tensions for each of the four caffeine exposures.

Effect of Ouabain on Submaximally Activated Arteries

Ouabain was found to potentiate the tone in nine arteries submaximally precontracted with norepinephrine. There was a significant increase in tension compared with the control group at every concentration of ouabain greater than 1 nM (Table 1 and Figure 6, top panel). The arteries were then incubated with the final concentration of ouabain (10 µM) for a further 16 minutes. During this period, the tension gradually fell, but at 16 minutes, it was still significantly greater than that in the control group (0.17±0.12 mN/mm for the ouabain group vs. 0.12±0.08 mN/mm for the control group; n=9, p<0.02) (Figure 6, middle panel).

The experiment in which eight vessels were submaximally precontracted with potassium showed a similar dose-response relation (Figure 6, bottom panel). Because these were carried out in the presence of 10 µM phentolamine, the possibility that this poten-

![Figure 5](http://hyper.ahajournals.org/)

**FIGURE 5.** Top panel: Recordings showing effect of 1-hour incubation in 10 µM ouabain on response to repeated 30-second exposures to 10 mM caffeine. Bottom panel: Line graph showing relative tensions achieved on serial exposure to 10 µM caffeine. Vessels were incubated in 10 µM ouabain, low sodium, or physiological saline solution (control) for 1 hour between the second and third exposures and thereafter.

The potentiating effect is due to the liberation of norepinephrine from perivascular neuromuscular junctions was effectively excluded.

**Discussion**

This study demonstrates that resting human resistance arteries from subcutaneous fat produce an increase in tone in response to incubation in ouabain and that this effect is time- and concentration-dependent. This effect was unlikely to be due to an action of ouabain at the neuromuscular junction as arteries exposed to ouabain and phenolamine generated a mean tension similar to that in arteries exposed to ouabain alone.26-28 However, ouabain-induced tone was attenuated by the addition of diltiazem, which, unlike some calcium antagonists,

<table>
<thead>
<tr>
<th>A.</th>
<th>Control</th>
<th>Ouabain (mean tension, mN/mm)</th>
<th>p</th>
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</thead>
<tbody>
<tr>
<td>Initial tension</td>
<td>0.72±0.11</td>
<td>0.77±0.12</td>
<td>NS</td>
</tr>
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<th>B.</th>
<th>Change in tension (mN/mm)</th>
<th>Ouabain</th>
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<tr>
<td>1 nM</td>
<td>-0.08±0.04</td>
<td>-0.06±0.06</td>
</tr>
<tr>
<td>11 nM</td>
<td>-0.10±0.06</td>
<td>0.10±0.08</td>
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<tr>
<td>0.111 µM</td>
<td>-0.11±0.06</td>
<td>0.32±0.13</td>
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<tr>
<td>10.1 µM</td>
<td>-0.14±0.06</td>
<td>0.61±0.15</td>
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Values are mean±SEM. Changes in tension were recorded after 4 minutes of exposure to ouabain. NS, not significant.
These results contrast with similar work in resistance arteries obtained from rat mesentery. Mulvany et al.\textsuperscript{13} showed that, after incubation in 1 mM ouabain, the intracellular sodium increased (by approximately 50 mM at 2 hours) and there was significant depolarization of the membrane (approximately 24 mV at 3 hours); yet there was no change in resting tension at 3 hours. The difference between their investigations and ours may therefore lie in the origin of the arteries, that is, either the vascular bed or the species. (Similarly, our findings in the human subcutaneous vascular bed may not reflect identical reactivity in other human vascular beds.) It may be that because of the relative insensitivity of rat tissue to cardiac glycosides,\textsuperscript{30,31} intracellular sodium rises more slowly in rat resistance arteries than in human resistance arteries. Alternatively, Na-Ca exchange may play a very minor role in the control of intracellular calcium in these experimental conditions.\textsuperscript{32-34}

Incubation in low external sodium also reduced the transplasmalemmal sodium gradient and resulted in a progressive increase in tension in our experiments. This is very similar to the effect of removing extracellular sodium in large artery preparations, which has been considered good evidence for the existence of Na-Ca exchange.\textsuperscript{11,12} In those experiments on rabbit and rat aortas, tension was found to increase progressively after the introduction of low sodium buffer, to reach a maximum within 20 minutes, and to reverse quickly within 5 minutes of the normalization of external sodium. In agreement with this work, we found immediate reversibility of the low sodium-induced tone. This suggested that reactivation of sodium-dependent calcium efflux by normalization of the transplasmalemmal sodium gradient expels excess accumulated intracellular calcium very promptly. It seems that not only is significant Na-Ca exchange present in human resistance arteries but also that it can make a very active response to a changing ionic environment. The relation between rising intracellular sodium and calcium may also be investigated by studying the intracellular calcium stores, particularly during the period before the development of tension. If a rise in intracellular sodium persists increases intracellular calcium, the extra calcium load will be buffered initially by the sarcoplasmic reticulum.\textsuperscript{35,36} The sarcoplasmic reticulum store was investigated in this study by the addition of caffeine, which unloads the caffeine-sensitive compartment.\textsuperscript{24} We found this to be increased after a 1-hour incubation with both low sodium and ouabain when tension had not yet developed.

The experiments in precontracted arteries, which arguably have more relevance to the in vivo situation, demonstrated a dose-dependent and immediate potentiation of tone in response to ouabain. The faster response to ouabain in precontracted arteries might be explained on the basis of the initial intracellular calcium concentration. The free cytoplasmic calcium in these arteries before the addition of ouabain would have been greater than that of the

\begin{figure}
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\includegraphics[width=\linewidth]{figure6}
\caption{Top panel: Line graph showing cumulative dose-response relation to ouabain for vessels submaximally precontracted with norepinephrine. \textit{p}<0.01, \textit{p}<0.005, and \textit{p}<0.001 compared with timed control. Middle panel: Line graph showing prolonged observation of the ouabain-induced (10 \textmu M) potentiation of submaximally contracted vessels (see top panel). \textit{p}<0.02, \textit{p}<0.005, and \textit{p}<0.001 compared with timed control. Bottom panel: Line graph showing cumulative dose-response relation to ouabain for vessels submaximally precontracted with potassium in the presence of 10 \textmu M phenolamine. \textit{p}<0.01 and \textit{p}<0.001 compared with timed control.}
\end{figure}

does not inhibit plasmalemmal electrogenic Na-Ca exchange (although it does inhibit brain and cardiac electoneutral mitochondrial Na-Ca exchange).\textsuperscript{29} Therefore, this finding suggests that a component (approximately 50% at only 6 hours) of the tone developed in the presence of ouabain is secondary to depolarization and calcium influx through potential-dependent channels but that there must also be another mechanism. As suggested by Blaustein,\textsuperscript{12} this may be inhibition of calcium efflux mediated by Na-Ca exchange.
resting arteries and might explain their enhanced response. Indeed, Aaronson and Benham have shown in guinea pig ureter smooth muscle that the elevation of intracellular calcium arising from reversal of the normal transplasmalemmal sodium gradient and mediated by Na-Ca exchange depends on the initial concentration of intracellular calcium. This possible mechanism was also discussed by Blaustein and Ashida.

In light of the work by Mulvany and colleagues, there may be an alternative explanation for the results in the precontracted vessels. In their experiments, ouabain also induced potentiation of tone of precontracted rat resistance arteries although, in contrast to our study, the effect was transient. They demonstrated that, although elevation of intracellular sodium in rat resistance arteries can occur very quickly after exposure to ouabain, the transient concentration-dependent potentiating action of ouabain was not dependent on it and indeed appeared to result from depolarization. This was deduced from experiments in low sodium buffer (25 mM) in which they demonstrated that ouabain-induced potentiation of tone was always associated with depolarization but was not always associated with change in intracellular sodium concentration.

In conclusion, in experimental situations in which Na-Ca exchange was maximally inhibited, human subcutaneous resistance arteries demonstrate a substantial increase in tension. Moreover, reactivation of Na-Ca exchange rapidly relaxed the arteries. Although these results do not directly demonstrate a physiological role for Na-Ca exchange in the control of resistance artery intracellular calcium, they argue strongly in favor of the presence of a potentially powerful exchange mechanism in these arteries.

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