Sodium Gradient, Smooth Muscle Tone, and Blood Pressure Regulation

By SYDNEY M. FRIEDMAN, M.D., PH.D., JAMES D. JAMIESON, AND CONSTANCE L. FRIEDMAN, PH.D.

Rat colon strips respond to an acute reduction of sodium concentration in the medium ($N_{la}$) by an immediate increase in tension, followed by relaxation to the basal tension as the tissue equilibrates. Following equilibration in low $N_{la}$ the responsiveness to drug-induced contraction is increased, while in high $N_{la}$ it is decreased. A contraction cycle, variously induced, can be aborted by the acute addition of sodium to the medium. The applicability of these findings to vascular smooth muscle in the whole animal can be demonstrated by appropriate acute sodium infusions. The effects in all cases can be referred to sodium, although modified by the anionic component of the salts used. The results are considered to support the view that smooth muscle tension is governed in part by the concentration gradient $N_{la}/N_{ai}$ and the theoretic implication of this for chronic hypertensive and hypotensive states is developed.

As a first general statement of the dynamic relation between sodium and vascular smooth muscle tone we have recently presented the theory that the sodium transfer systems, broadly defined, are primary determinants of the blood pressure.\textsuperscript{1,2} Although this is based on the observed association between cation shifts and acute changes of blood pressure, we have argued that it is pertinent to chronic changes as well.\textsuperscript{3} Further study of the problem has divided itself into two phases, exploration of the endocrine mechanisms regulating sodium transfers, and exploration of causality in the association of sodium transfers and smooth muscle tonus.

Exploration of the endocrine mechanisms has been confined to the neurohypophysis and mineralocortex, since these are primary regulators of salt and water balance and, not surprisingly, of blood pressure as well. Our studies have followed the usual endocrinologic approach, dealing in turn with the effects of hyposecretion and hypersecretion. Thus shifts in sodium, potassium, and water were followed in association with the changing blood pressure pattern, (a) in adrenalectomy,\textsuperscript{4} (b) in neurohypophysial denervation,\textsuperscript{5} (c) after pitressin injection,\textsuperscript{6} and (d) after aldosterone injection.\textsuperscript{7}

These observations systematically led to the conclusion that the sodium concentration (activity) gradient between the outside ($N_{la}$) and inside ($N_{ai}$) of the smooth muscle cell is a basic determinant of tone, an increase in gradient ($N_{la}/N_{ai}$) leading to a decrease in tone, a decrease in gradient to an increase in tone.\textsuperscript{3} The blood pressure setting from low to high values is viewed as depending on graded changes in sodium transfer equilibria.

The levels of secretion from mineralocortex and neurohypophysis were found to be inversely related, acting in the same direction on the sodium gradient and homeostasis. In consequence, a decreased secretion from the one demands hyperfunction of the other as compensation.\textsuperscript{4,5}

This position, a more specific one than the first general statement of our theory, predicted that smooth muscle tension could be varied by altering the sodium gradient and that this should be especially applicable to small blood vessels. It thus predicted that blood pressure would fall, or an induced pressure rise be aborted, if the sodium gradient were acutely raised as, for example, by the

\textsuperscript{From the Department of Anatomy, The University of British Columbia, Vancouver, Canada.}

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rapid infusion of a sufficient quantity of sodium. The core of the problem was thus to induce acute changes in gradient so rapidly that we could be sure that only the gradient had been altered. Observations could then be made both on the effects of the imposed change and on the subsequent expected restoration of equilibrium. Our approach has thus been to manipulate Na₀ as rapidly as possible both in vitro and in vivo.

For the in vitro examination of the postulates, colon smooth muscle was used, since this tissue responds readily to drugs in dose ranges corresponding to those used in vivo. Unfortunately, it is not possible to secure vascular strips from the peripheral arteriolar bed for similar studies. For this reason, the responses of vascular smooth muscle were tested directly in the whole animal.

Evidence to show that a change in sodium gradient is associated with a change in smooth muscle tension both in colon and in the peripheral vascular bed is here presented, together with a discussion of the theoretic implications of the findings.

Methods

In Vitro Colon Strip. The distal 7 cm. of colon from mature male albino rats was excised under ether anesthesia, slit open along the mesenteric attachment, washed clean with, and then stored for 30 min. at room temperature in, buffered medium. The tissue was then mounted on a strain gage tensometer and allowed to equilibrate a further 1.5 hours in the buffer before use. A basal tension of 20 microinches/inch (12 gm/in. equivalent to 1 Gm.) was then applied and the tissue stimulated repeatedly with threshold doses of carbachol until steady reproducible responses were obtained. The tension was left unaltered throughout the course of the experiment.

The basic buffered medium used throughout was a modified Krebs-Henseleit solution containing 200 mg per cent glucose, and with the following ionic composition in mEq./L.: NaCl 129.0, KCl 5.0, CaCl₂ 4.2, MgSO₄ 2.4, NaH₂PO₄ 1.2, NaHCO₃ 25.0. The total Na content was thus 155 mEq./L. All solutions were continuously aerated with 5 per cent carbon dioxide in oxygen to pH 7.4. Sodium-deficient solutions were restored to isosmolarity with sucrose (2 mM of sucrose for each decrease of 1 mEq. NaCl). All experiments were carried out at room temperature.

In Vivo. The basic plan was to infuse salt solutions of known Na concentration and pH at fixed rates for predetermined periods of time into the femoral vein of the mature male rat. All infusions were given at the standard rate of 0.005 ml/sec. for times varying between 0.5 and 3.5 min. (0.15 ml. to 1.85 ml.). Blood pressure was recorded continuously and electromanometrically from the femoral artery. All operative procedures were carried out under light ether anesthesia.

Results

I. In Vitro

The Effect of an Acute Reduction in External Na (Na₀) on Colon Strip Tension. A series of aerated solutions with Na reduced from the base of 155 mEq./L. in steps of 12 to 78 mEq./L. was prepared. These could be exchanged within a few seconds. After equilibration of the tissue at 155 mEq./L. as described, the next lower bath (143) was substituted, the response recorded, and the tissue then returned to the 155 mEq./L. bath for a 5 min. rest. This sequence was repeated for the full series of low Na baths. Five separate experiments covering this range in whole or in part were carried out. Representative data, plotted directly from the recordings without smoothing, are shown in figure 1.

In all cases, the acute reduction of Na₀ was followed at once by a spontaneous contraction and subsequent gradual relaxation back to the basal tension. The degree of contraction was a function of the degree of reduction in Na₀.
FIG. 2. Rat colon. 0.012 µg./ml. carbachol as stimulus. Effect in control medium of 155 mEq./L. of Na compared with effect in 167, 179, and 191 mEq./L. from above down to show progressive delay in onset and decrease in amplitude of contraction. Attenuation factors: X 2, X 5.

Since the contraction occurred promptly upon contact of the tissue with the low Na medium, it is unlikely that Na, was affected. Effectively then, the tissue contraction is a response to the reduced Na, sodium gradient. Reasons will be given for suggesting that the relaxation phase represents a restoration of the gradient due to a decrease in Na,.

No tension change followed the mere mechanical exchange of one bath for another of the same composition. Tension increases have also been recorded following lowering of the external Na concentration in steps of 3 and 6 mEq./L.

These results thus support the first prediction that smooth muscle tension can be varied by altering the Na concentration gradient.

Effect of Reduced Na, on Drug-Induced Contraction of Colon Strip. If drug-induced contraction is similarly caused by an alteration in Na gradient, as our previous work implies,¹ and if a given dose moves a given quantity of Na, then the effect on the gradient will increase as Na, falls. Equilibrium in low Na medium presumably lowers Na, and thus would be expected to heighten the response to drug-induced contraction.

In 2 experiments, a threshold dose of carbachol was used as stimulus after 3 min. of equilibrium in various low Na media. The results, shown in table 1, clearly demonstrate a heightened response to the carbachol stimulus in low Na media.

The Effect of an Acute Increase in Na, on Colon Strip Tension. The same plan was used as before, the exchange baths containing 167, 179, 203 and 310 mEq./L. of Na, respectively. As control, a bath with added sucrose, equivalent in tonicity to the addition of 25 mEq./L. of Na was prepared. As before, the sequence was to equilibrate at base (155), then to record

<table>
<thead>
<tr>
<th>Sodium concentration (mEq./L.)</th>
<th>Maximum tension (cm.)</th>
<th>Change</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Base</strong></td>
<td><strong>Test</strong></td>
<td><strong>Base</strong></td>
</tr>
<tr>
<td>155</td>
<td>143</td>
<td>11.5</td>
</tr>
<tr>
<td>155</td>
<td>143</td>
<td>9.0</td>
</tr>
<tr>
<td>155</td>
<td>131</td>
<td>12.0</td>
</tr>
<tr>
<td>155</td>
<td>131</td>
<td>9.6</td>
</tr>
<tr>
<td>155</td>
<td>110</td>
<td>12.0</td>
</tr>
<tr>
<td>155</td>
<td>107</td>
<td>11.5</td>
</tr>
<tr>
<td>155</td>
<td>107</td>
<td>11.5</td>
</tr>
<tr>
<td>155</td>
<td>95</td>
<td>9.6</td>
</tr>
<tr>
<td>155</td>
<td>78</td>
<td>10.5</td>
</tr>
<tr>
<td>155</td>
<td>78</td>
<td>12.0</td>
</tr>
</tbody>
</table>

*The response of each strip was determined in both base and test medium.
the response in the test medium, followed by a return to base for a rest of 5 min. No spontaneous change in tension was noted in any bath, although the tissue was observed for 1.5 min. Each time that the tissue was returned to base after this seemingly brief immersion in the high Na medium, however, a spontaneous contraction occurred. Apparently, equilibration in high Na increases Na as well, so that on return to the lower Na of the base bath the ratio Na/Na is suddenly reduced and a contraction follows, just as it does when Na is reduced experimentally.

Effect of Increased Na on Drug-Induced Contraction of Colon Strip. If our previous reasoning, that drug-induced contraction also operates through a reduction in gradient, is correct, and if a given dose moves a given quantity of Na, then the drug should be less effective after equilibration in high Na baths.

In a series of tests, carbachol was used 30 sec. after the tissue had been moved to higher Na. A typical effect is shown in figure 2. The response was delayed in onset, and it decreased in magnitude proportionately as Na was increased; at Na concentration of 191 mEq./L, no contraction at all could be induced. Five minutes after restoring the tissue to the base solution, normal responses were again obtained. The addition of sucrose in an amount osmotically equivalent to an increase of 25 mEq./L. of Na was without effect on the response to carbachol. These results are thus the counterpart of those showing increased sensitivity after equilibration in low Na media.

Effect of Acutely Raising Na During Drug-Induced Contraction of Colon Strip. By this time there was little doubt that acute changes in Na gradient could change smooth muscle tension. It also seemed likely that drug-induced contraction operated through such gradient changes. If this were in fact so, then it would be expected that the sudden addition of Na to the medium during contraction would restore the reduced gradient and so abort the contraction.

This critical postulate was tested in a series of experiments in which Na in amounts sufficient to raise Na by 15 mEq./L. was added acutely at various stages of contraction. All experiments were internally controlled as before, the standard response determined first, the test runs thereafter. The tissue was allowed 3 min. in the base solution (155) between runs. All experiments in replicate runs yielded the same result, and typical findings are shown in figures 3 and 4. The effect of Na in aborting contraction is sudden and dramatic. The general nature of the response is shown by the
fact that it occurs as readily with contraction induced by reduction of Na in the medium as with serotonin or carbachol. Osmotically equivalent sucrose failed to replace sodium in the reaction (fig. 5). Sodium phosphate was more effective, and sodium acetate less effective, than sodium chloride in interrupting contraction. We conclude that, while Na is specific, its effects are modified by the associated anion.

II. In Vivo

The described experiments were based on the premise that smooth muscle tension is determined by Na gradient. They demonstrated that this is so both for spontaneous and for drug-induced contraction in colon smooth muscle. The results, however, have limited application unless they can be shown in vascular smooth muscle as well. Unfortunately, it is almost impossible to obtain a suitable in vitro preparation of peripheral vascular tissue. We therefore proceeded to the whole animal. Here there is no ready means for inducing an acute reduction of Na, but there are other ways of testing the role of gradients. Thus, using diastolic blood pressure as an index of vascular smooth muscle tone, it would be expected (a) that the acute elevation of Na by infusion would increase the gradient and so depress the blood pressure, (b) that drug-induced pressor responses would be aborted by the acute infusion of Na after vasoconstriction had started, and (c) that the effectiveness of pressor agents would be reduced in the presence of an increase in Naω induced before the drug was applied.

The Effect of an Acute Infusion of Na on the Blood Pressure. Sodium acetate, lactate, or phosphate was infused into groups of at least 8 rats for each. All infusions were carried out at the standard rate of 0.005 ml/sec. for 2.5 min. in the case of 2 mEq/ml. solutions, for 3.5 min. in the case of 1 mEq/ml. salts. The amounts of Na infused related to the blood pressure record are shown in table 2. The results were consistent and similar for all salts. All infusions produced a fall in pressure as expected, beginning after the infusion of approximately 200 μEq/100 Gm. (about 8 per cent of the total calculated extracellular Na), regardless of the concentration of the solution. Usually a rise in pressure occurred shortly after the beginning of the infusion; this is not due to vasopressin release, since it also occurs in neurohypophysectomized animals. This rise was always transient and always yielded to a fall in pressure, continuous in slope as long as the infusion continued. On cessation of the infusion, the pressure promptly returned to normal levels.

Figure 6 shows typical pressure responses and also the failure of a control infusion of sucrose to produce the depressor effect. The depressor effect of infused Na was even greater in the case of DCA-hypertensive rats. The effect was not particularly pH-dependent, although it was most sharply demonstrated with solutions above pH 7.0. It is anion-dependent, since no effect was observed either with sodium chloride or sodium sulfate infused at corresponding concentrations. It is not mediated by the autonomic nervous system, since it can be even more readily demonstrated in animals pretreated with either dibenzyline or hexamethonium salt.

The Effect of an Acute Infusion of Na Following Drug-Induced Blood Pressure Elevation. Blood pressure was raised by the intravenous injection of 75 milliunits of pitressin in 0.1 ml. of saline, and control measurements were made of the pressor effect. Following this, sodium phosphate infusions (1.5 mEq/ml., pH 7.2, 0.005 ml/sec.) were carried out, beginning at varying times in the pressor
cycle, i.e., at the same time as the pitressin injection, or 10 or 20 sec. later. In each rat a control run and one or more runs with infusion were carried out. (Tachyphylaxis to pitressin did not occur under these circumstances.) A similar procedure was repeated using 0.5 μg. of norepinephrine in 0.1 ml. of saline injected intravenously over a 30 sec. interval. Groups of at least 8 rats were used for each pressor agent.

Typical effects are shown in figure 7. The infusion of Na always reduced and aborted the pressor response, the effect usually being observed after the infusion of about 200 μEq./100 Gm. The amounts of Na involved were of the same order of magnitude as we have previously shown to leave the extracellular compartment during a pressor response. The effectiveness of Na is again modified by the associated anion; thus, phosphate, glutamate and acetate were effective in decreasing order.

The Effect of an Acute Infusion of Na Preceding Drug-Induced Pressor Responses. We have already reported experiments showing that the infusion of Na, in an amount which itself does not affect blood pressure, depresses the response both to pitressin and to norepinephrine. The at the time of these experiments we had no explanation of our observations. Since we had now demonstrated and explained this effect for in vitro experiments, the characteristic in vivo response was again demonstrated for this report, to complete the comparison. The same infusion of sodium phosphate as in the previous experiment was used, this time given for 2 min. before injecting the pressor agent, either 30 milliunits of pitressin or 0.5 μg. of norepinephrine. The depression of pressor response is shown in figure 8.

DISCUSSION

In previous experiments we observed a clear association between shifts of sodium and acute elevation or depression of the blood pressure. Extracellular sodium decreased as pressure rose or increased as pressure fell. Inverse movements of potassium in lesser amounts usually but not invariably (e.g., angiotensin) accompanied these sodium changes. We argued that these transfers of sodium were regulators of blood pressure, that is, of vascular smooth muscle tone. Substantive evidence for this contention has been presented in this report. Using rat colon as a representative smooth muscle system, we have shown that the acute reduction of sodium in the medium is a potent stimulus to contraction, indicating that the fall in extracellular sodium in the whole animal is causal to the pressor effects.

The in vitro investigation of the colon strip led to further conclusions. When the tissue was rapidly exposed to a low sodium medium, it seemed probable that Na<sub>a</sub> (intracellular sodium) had not been altered. In effect, the stimulus here was an acute decrease of the concentration gradient Na<sub>a</sub>/Na<sub>e</sub>. If this were indeed so, and if contraction in general operates through such a mechanism, then it follows that a contraction, no matter how induced, can be aborted by the acute addition of sufficient sodium to restore the normal gradient. This was shown to be the case both in vitro for the

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**Table 2.** The Effect on Blood Pressure in the Intact Rat of Sodium Salts Infused Intravenously at 0.005 ml./sec.

<table>
<thead>
<tr>
<th>Infusion</th>
<th>No. of rats</th>
<th>Average wt. (Gm.)</th>
<th>Basal pressure</th>
<th>Total Na infused (mEq.)</th>
<th>mm. Hg fall before fall (mEq.)</th>
<th>Na infused/100 Gm. before fall (mEq.)</th>
<th>pH</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sodium acetate,</td>
<td>8</td>
<td>288±8</td>
<td>116±7</td>
<td>84±3</td>
<td>1.5</td>
<td>20±6</td>
<td>0.21±0.02</td>
</tr>
<tr>
<td>2 mEq./ml.</td>
<td></td>
<td></td>
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<td></td>
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</tr>
<tr>
<td>Sodium lactate,</td>
<td>8</td>
<td>292±7</td>
<td>126±3</td>
<td>78±3</td>
<td>1.5</td>
<td>23±3</td>
<td>0.15±0.02</td>
</tr>
<tr>
<td>2 mEq./ml.</td>
<td></td>
<td></td>
<td></td>
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<td></td>
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</tr>
<tr>
<td>Sodium phosphate,</td>
<td>7</td>
<td>274±8</td>
<td>119±8</td>
<td>72±5</td>
<td>1.5</td>
<td>49±9</td>
<td>0.24±0.03</td>
</tr>
<tr>
<td>2 mEq./ml.</td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sodium phosphate,</td>
<td>8</td>
<td>255±5</td>
<td>126±2</td>
<td>78±2</td>
<td>1.05</td>
<td>20±2</td>
<td>0.20±0.01</td>
</tr>
<tr>
<td>1 mEq./ml.</td>
<td></td>
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</table>
colon strip and in vivo for the vascular system. In vitro, the addition of sodium aborted contraction, whether induced by carbachol, serotonin, or by acutely lowered Na, while in vivo the infusion of sodium aborted both pitressin-induced and norepinephrine-induced pressor responses. It seems reasonable to suggest that normal relaxation occurs by a restoration of gradient.

Further correlation between the in vitro colon strip and the whole animal's vascular system was obtained with the demonstration that equilibration in high sodium media, which presumably causes a proportionate increase in Na, reduced the response to constrictive stimuli, an observation which we had made before in relation to blood pressure, but for which we then had no explanation. A given amount of constrictor drug apparently can shift a given amount of Na. This shift produces a greater change in the gradient Na/Na when Na is low than when it is high, whence the reduced response in high sodium media, the increased response in low sodium media.

There can be little doubt that the sodium transfer systems are primary determinants of smooth muscle tone, although the effects may be modified in as yet unclear ways by the associated anions. Further, a tissue equilibrated in media of varying sodium concentration should maintain normal tone within wide limits as long as a normal gradient is maintained. On the other hand, for the whole animal, the limits of "sodium gradient excursion" represent the limits of blood pressure excursion. This provides a rational approach to the well known "ceiling" and "floor" phenomena for pressor and depressor agents and the dependence of the response on the basal setting.10

It seems worth while to develop the concept of "gradient excursion" more fully, since it suggests an approach to the understanding of

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**Fig. 6** Left. A. Sucrose 1 M infused intravenously at 0.005 ml/sec. in normal adult male rat. B. Sodium acetate, pH 6.7, 7.5 μEq. Na/sec. (1.5 mEq./ml. X 0.005 ml/sec.) in normal adult rat. C. Sodium phosphate, pH 7.2, 7.5 μEq. Na/sec. (1.5 mEq./ml. X 0.005 ml/sec.) in normal adult male rat. D. Sodium phosphate, as in C, in DCA hypertensive rat.

**Fig. 7** Right. A. 75 μg. pitressin in 0.1 ml. saline intravenously in normal adult male rat. B. 75 μg. pitressin intravenously followed immediately by sodium phosphate infusion, pH 7.2, 7.5 μEq. Na/sec. (1.5 mEq./ml. X 0.005 ml/sec.). C. 0.5 μg. norepinephrine in 0.1 ml. saline intravenously slowly over 30 sec. D. 0.3 μg. norepinephrine followed immediately by sodium phosphate, as in B.
blood pressure regulation, especially in chronic aberrations, and offers a rationale for further experiments. The basic features of this concept are given in figure 9.

Let the basal or normal diastolic blood pressure (= peripheral vascular smooth muscle tone) correspond to a concentration gradient represented by the slope AB. Because there is far less sodium within the cell than outside, this slope is steep (drawn here at 1-10, although 1-14 is probably a better approximation), so that a small change in \( \text{Xa}_1 \) corresponds to a large change in \( \text{Na}_o \). Within a presumably narrow range, zone 1, \( \text{Na}_o \) may increase from \( \text{Xa}_1 \) to \( \text{Xa}_2 \), and \( \text{Na}_o \) may adapt readily by moving the proportionately larger distance of \( \text{Y}_1 \) to \( \text{Y}_2 \). As \( \text{Na}_o \) moves further towards \( \text{Xa}_\max \) however, \( \text{Na}_o \) is less and less able to keep pace, the gradient \( \text{Na}_o/\text{Na}_1 \) decreases, and pressure must rise as demonstrated. This gradual change, shown as zone 2, would occur if, for any pathological reason, \( \text{Na}_1 \) accumulated. Conversely, as \( \text{Na}_1 \) decreases towards \( \text{Xa}_\min \), \( \text{Na}_o \) fails to fall proportionately, the gradient \( \text{Na}_o/\text{Na}_1 \) increases, and pressure falls. This change, shown as zone 3, would be expected to occur if, for any pathological reason, \( \text{Na}_1 \) were depleted. The maximum possible blood pressure excursion is defined by the 2 extreme gradients \( \text{Xa}_\min/\text{Xa}_\max \) and \( \text{Y}_\max/\text{Xa}_\min \), but since \( \text{Xa}_\max \) and \( \text{Xa}_\min \) represent pathological extremes, it is most likely that ordinary acute excursions of blood pressure occur in zone 1 in the area between the limits \( \text{Y}_1/\text{Xa}_2 \) and \( \text{Y}_2/\text{Xa}_1 \). The blood pressure response would always depend on the initial \( Y/X \) ratio.

This scheme provides a reasonable explanation for several observations. Thus, in adrenalectomy, it has been suggested that the
primary defect is a rapid depletion\textsuperscript{11,12} of Na\textsubscript{o}. This is countered, as expected, by a fall in Na\textsubscript{o} which cannot keep pace (zone 3), and pressure falls. That the observed fall in Na\textsubscript{o} is indeed homeostatic and dependent on neurohypophysial hyperfunction has been well demonstrated.\textsuperscript{13,14} We have confirmed this and found that in the absence of neurohypophysal function not only does Na\textsubscript{o} fail to fall after adrenalectomy, but blood pressure drops precipitously and the animal succumbs early. As expected, the addition of salt to the diet increases both Na\textsubscript{i} and Na\textsubscript{o} back towards zone 1, the favorable part of the range.

Similarly, in salt-dependent hypertensive states, the basic defect favors an increase in Na\textsubscript{i}\textsuperscript{13} with which Na\textsubscript{o} cannot keep pace and pressure rises (zone 2). If Na\textsubscript{o} is assisted in increasing further by the acute infusion of Na\textsubscript{i}, blood pressure, as we have shown, falls promptly. This is an instructive demonstration but, of course, in the long run such treatment would be deleterious, since with equilibration Na\textsubscript{i} would increase further. More physiologically, chronic salt-depleting procedures gradually reduce both Na\textsubscript{i} and Na\textsubscript{o} back towards the favorable range of zone 1.

There is also good evidence that excessive sodium depletion can lead to vascular collapse (zone 3), and there is evidence that a long-continued high salt diet may produce hypertension (zone 2).

The concept of "gradient excursion" thus considers the limits of blood pressure to be determined by the limiting relations between Na\textsubscript{i} and Na\textsubscript{o} and stresses Na\textsubscript{i} particularly. It suggests that no correlation is to be expected between blood pressure and either Na\textsubscript{i} or Na\textsubscript{o} examined alone. Whether this concept links sodium concentration gradients to blood pressure or not, certainly the experiments reported here show clearly that such gradients are causally linked to smooth muscle tension both in gut and in the vascular tree.

**Summary**

The effect of sodium on smooth muscle tension was studied in vitro by the direct measurement of tension in a rat colon strip. The dependence of the muscle tension on the Na\textsubscript{o}/Na\textsubscript{i} gradient was demonstrated. The acute reduction of Na\textsubscript{o} (medium) was followed at once by a spontaneous contraction and subsequent gradual relaxation back to the basal tension. The degree of contraction was a function of the degree of reduction of Na\textsubscript{o}. Drug-induced contraction was Na dependent, since responsiveness was increased by prior equilibration in low Na\textsubscript{o} and decreased by high Na\textsubscript{o}. A contraction once started, whether induced by the acute reduction of Na\textsubscript{o} or by a constricting agent, could be specifically aborted by the addition of Na to the medium.

The general applicability of these findings to vascular smooth muscle was demonstrated in the whole animal using the diastolic blood pressure as an index. The acute infusion of Na salts produced a fall in blood pressure which was related to the amount of Na infused. The acute infusion of Na consistently aborted pitressin or norepinephrine-induced pressor responses. The infusion of Na in amounts insufficient to affect the blood pressure reduced the sensitivity to pressor agents.

The conclusion is drawn that the Na gradient is a major determinant of peripheral vascular resistance and the theoretical implications of this for chronic hypertensive and hypotensive states is elaborated.

**Summario in Interlingua**

Le effecto de natrium super le tension de musculo lisie esseva studiate in vitro per le mesuration directe del tension in un segmento del colon de un rato. Esseva demonstrate le facto que le tension muscular depende del gradiente de natrium inter medio e musculo (Na\textsubscript{o}/Na\textsubscript{i}). Le reduction acute de Na\textsubscript{o} esseva sequite immediatemente per un contraction spontanea con subsequente relaxation gradual usque al tension de base. Le grado del contraction esseva un function del grado de reduction de Na\textsubscript{o}. Le induction de contractiones per medio de drogas dependeva del presentia de natrium: le responsivitate esseva augmentate per le previe equilibration in Na\textsubscript{o} basse e reduceque per Na\textsubscript{o} alte. Un contraction in progreso—sin reguardo a si illo habeva essite
SODIUM GRADIENT AND SMOOTH MUSCLE TONE

... induce per un reduction de Na, o per un agente de constriction—poteva esser disrumpite specificamente per le addition de Na al medio.

Le applicabilitate general de iste constatazioni al muscolo lisie del vasculatura eseva demonstrate in animales intacte con le uso del pression de sanguine diastolic como indice. Le infusion acute de sales de natrium produceva un reduction del pression de sanguine in correlation con le quantitate de natrium infundite. Le infusion acute de natrium disrumpeva regularmente le responsas pressori induce per pitressina o norepinephrina. Le infusion de natrium in quantitates non sufficiente pro afficer le pression de sanguine sufficiente pro reduce le sensibilitate a agentes pressori.

Es concludite que le gradiente de natrium es uu determinante major del resistencia periphero-vascular. Le inherente consequentias de isto, con respecto al statos de hyper- e hypo-tension chronic, es disveloppate.

REFERENCES