Local Effects of Sodium, Calcium and Magnesium Upon Small and Large Blood Vessels of the Dog Forelimb

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Resistance to blood flow through the small vessels of the dog foreleg decreased following local elevation of serum sodium and magnesium concentrations. Small vessel resistance increased following elevation of calcium concentration. Associated with the former changes was decreased responsiveness to levarterenol and methacholine. These changes likely result from effects of the cations upon the smooth muscle cell of the arteriole.

Numerous studies indicate that the major cations (H⁺, Na⁺, K⁺, Ca²⁺, Mg²⁺) influence the function of many types of cells. Their effect upon the function of the smooth muscle cell of the arteriole is of particular interest to vascular physiologists because this cell controls the main variable resistance to blood flow. The methods of study of this cell, by necessity, have been indirect. These methods may be classified into 4 types. The types are change of cation content generally within an animal while observing blood pressure, blood flow or resistance to flow,¹⁻¹¹ local change of cation concentration in blood while observing flow of blood or resistance to flow,¹² change of concentration in an artificial fluid perfusing an isolated vascular bed while observing resistance to flow,¹³⁻¹⁶ and change of concentration in an artificial fluid surrounding an isolated large vessel while observing tension or length.¹⁷⁻²¹ These methods do not conclusively indicate the direct effect of the cation upon the smooth muscle cell of the arteriole. The first method fails to distinguish between direct and remote effects and does not localize effects to the arteriole.

The second method may eliminate remote effects, but, even with this method, the effects are not necessarily localized to the arteriole. Total resistance across a bed may change in a direction opposite to arteriolar resistance.²² The same criticism may be applied to the third method, and, in addition, it suffers from the inadequacy of an unphysiologic perfusion fluid. As to the fourth method, the danger of transference of results from isolated large vessels bathed in artificial fluids to the arteriolar smooth muscle cell in intact circuits is obvious.

In view of the above, it seemed profitable to vary the concentration of cations locally while measuring a parameter which more nearly indicates function of the smooth muscle cell of the arteriole. The parameter selected was resistance to blood flow across the small blood vessels of the dog foreleg.²² The resistance across this vascular segment is primarily offered by the arteriole. We have previously reported that small vessel resistance falls as the local serum concentration of potassium is elevated.²³ When concentration is also raised in the body, increase of large arterial resistance, likely due to an adrenal discharge, occurs simultaneously with decrease of small vessel resistance. The present report concerns the local effects of the sodium, calcium, and magnesium ions.

Methods

Various sodium, calcium, and magnesium salts were infused into the brachial artery of the dog at rates which significantly raised the concentrations of the cations in the foreleg but which did not sig-
significantly change the concentrations in the body. Their effects upon calibers of arteries, small vessels and veins in the foreleg were inferred from changes of pressure gradients during constant flow of blood into the leg. Pressure gradients were calculated from pressure measurements at 4 sites along the length of the bed. Responsiveness of the vessels at various cation concentration levels was assessed by injecting levarterenol (norepinephrine) bitartrate and methacholine chloride into the brachial artery.

The study includes a total of 97 infusions in 72 dogs. The animals weighed 14 to 18 kg, and were anesthetized by intravenous injection of sodium pentobarbital, 25 mg./Kg. Following intravenous injection of 70 mg. heparin sodium, a pre-calibrated blood pump was interposed between the proximal segment of the ligated left femoral artery and the distal segment of the ligated right brachial artery. The output of the pump was independent of pressure over the ranges encountered. A flow rate was selected which produced a mean pressure in the distal brachial artery similar to that in the aorta. At this pressure, flow rate varied from 45 to 100 ml./min. in different animals but was maintained constant throughout an experiment in a given animal. Needles were inserted into the brachial artery distal to the pump and cephalic vein at the level of the elbow. Glass tubes, with an outside diameter of 0.5 mm., were passed distally into a small artery of the footpad and small vein of the dorsal subcutaneous tissue of the paw. These methods have been described and defended in detail in previous communications. The needles and tubes were attached, through a multiple stopcock arrangement, to a pressure transducer. A catheter was threaded up the proximal segment of the brachial artery to the arch of the aorta. This was attached to a second transducer. A catheter was threaded up the proximal segment of the brachial artery to the arch of the aorta. This was attached to a second transducer.

Ten per cent solutions of sodium chloride, sodium bicarbonate, sodium lactate, sodium sulfate, calcium chloride, calcium lactate, calcium sulfate, and magnesium sulfate were separately infused into the brachial artery at rates ranging between 0.1 and 2.3 ml./min. Pressures were measured after they became steady. This usually obtained within one minute of starting an infusion or changing the rate of infusion. Blood was withdrawn from the cephalic vein and a hindleg vein before, during, and after infusion for determination of cell fraction and serum cation concentrations. Levarterenol 0.25 to 1.00 y, and methacholine chloride 0.50 to 1.00 y, were periodically injected into the brachial artery and the effects upon brachial arterial pressure continuously recorded.

Serum sodium and potassium concentrations were determined with a Baird flame photometer, calcium concentration by the method of Clark and Collip, and magnesium concentration by the method of Briggs. Pressure gradients from brachial artery to cephalic vein, brachial artery to small artery, small artery to small vein, and small vein to cephalic vein were determined. Resistances to blood flow across the entire foreleg vascular system, through arteries (5.0 to 0.5 mm.), small vessels (less than 0.5 mm.), and veins (0.5 to 5.0 mm.) were calculated by dividing the respective pressure gradients by the rate of blood flow in the brachial artery.

Results

Sodium (34 animals)

Ten per cent solutions of sodium chloride, sodium lactate, sodium bicarbonate, and sodium sulfate were separately infused, in randomized sequence, into the brachial arteries of 8 dogs. The rates of infusion were 0.3, 0.6, and 1.0 ml./min. in that order. Each salt progressively depressed brachial and small arterial pressures without affecting venous pressures. The pressures returned to control levels shortly after stopping the infusions. Sodium chloride was selected for detailed study. The hematocrit of cephalic venous blood was determined in 3 animals before, during, and after infusion of 0.8 ml./min. of 10 per cent sodium chloride into the brachial artery. Though brachial and small arterial pressures fell during infusion in each instance, hematocrits did not change significantly. Eight animals received 0.3, 0.6, and 1.0 ml./min. 10 per cent sodium chloride into the brachial artery over a 10 min. period. These infusion rates delivered 0.5, 1.0, and 1.7 mEq. Na+/min. respectively. Results are presented in table 1. Arterial pressures, total resistance, and small vessel resistance decreased as a function of the infusion rate. These changes disappeared within 5 min. of stopping the infusion.

With these data as a background, 11 animals were studied in order to relate serum sodium concentration to the vascular events and to determine the effect of the sodium ion upon responsiveness of the bed to levarterenol and methacholine. Ten per cent sodium chloride...
CATIONS AND BLOOD VESSELS

Table 1
Average Effect of 10% NaCl Infused into Brachial Artery upon Foreleg Vascular Pressures and Resistances* in 8 Dogs.

<table>
<thead>
<tr>
<th>Infusion Rates</th>
<th>Brachial Arterial Pressure</th>
<th>Small Arterial Pressure</th>
<th>Small Venous Pressure</th>
<th>Cephalic Venous Pressure</th>
<th>Total Resistance</th>
<th>Arterial Resistance</th>
<th>Small Vessel Resistance</th>
<th>Venous Resistance</th>
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<td>mm. Hg</td>
<td>mm. Hg</td>
<td>mm. Hg</td>
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</table>

*Calculated separately for each animal and then averaged.
†Brachial arterial blood flow held constant at average value of 79 ml./min.
§Just before starting infusion.
§§Five min. after stopping infusion.

was infused into the brachial artery at 1.0 and 2.3 ml./min. These infusion rates delivered 1.7 and 3.9 mEq. Na+/min. respectively. The effects upon pressures, resistances, and serum sodium and potassium concentrations of cephalic venous blood are presented in fig. 1. Arterial pressures, total and small vessel resistances, and potassium concentration decreased as local sodium concentration was increased over ranges which might occur naturally. Serum sodium and potassium concentrations in hindleg venous blood at the end of the infusion averaged 152 and 3.4 mEq./L. respectively. Aortic pressure did not change. The responsiveness of the system to vasoactive substances appeared to progressively decrease as the sodium concentration was elevated (fig. 2). This was manifest in intensity as well as duration of change of brachial arterial pressure in 8 of 10 tests with levarterenol, and 6 of 9 tests with methacholine chloride. On the average, 0.5 to 1.0 g levarterenol injected into the brachial artery before infusion of sodium chloride increased the area under the brachial arterial pressure curve 10.4 sq. cm. During infusion at the rate of 2.3 ml./min. and 5 min. after stopping the infusion, the increases were 6.6 and 8.6 sq. cm. respectively. Corresponding decreases as a result of injection of 0.5 to 1.0 g methacholine chloride were 2.4, 1.8 and 3.3 sq. cm. respectively. These changes are similar to those produced by infusion of potassium.25

Four animals were studied before and after section of all foreleg nerves just below the brachial plexus25 and after section of nerves plus local adrenergic blockade. Adrenergic blockade was accomplished by infusing phenolamine methanesulfonate at the rate of 50 μg/min. into the brachial artery. This infusion rate is sufficient to prevent a response to a challenging injection of 0.5 g levarterenol into the brachial artery. Sodium chloride (0.6 to 4.0 mEq. Na+/min.) into the brachial artery decreased total and small vessel resistance under each of the 3 conditions. In one leg with a blood flow rate of 75 ml./min., 4.0 mEq. Na+/min. decreased total resistance from 1.61 to 0.99, 1.24 to 1.00, and 1.15 to 0.91 mm. Hg/ml./min. before nerve section, after nerve section and after nerve section plus phenolamine respectively.

Calcium (39 animals)

Ten per cent solutions of calcium chloride, calcium gluconate and calcium lactate were separately infused, in randomized sequence, into the brachial arteries of 14 dogs. The rates of infusion were 0.3, 0.6, and 1.0 ml./min. in that order. Each salt raised arterial pressures without affecting venous pressures. The pressures remained elevated for long periods after stopping the infusions. The actions of the 3 salts did not appear to be greatly different. Calcium chloride was selected for detailed study. The hematocrit of cephalic venous blood was determined in 3 animals before,
Figure 1
Relation of serum sodium concentration to vascular pressures and resistances in the dog foreleg. Average of 11 animals. Blood flow rate in the brachial artery held constant at average value of 115 ml./min. Ten per cent sodium chloride infused into brachial artery at 0.0, 1.0, 2.3 and 0.0 ml./min. in that order. Pressures measured after they became steady. Sodium and potassium concentrations are those in cephalic venous serum of the same leg. Serum sodium and potassium concentrations in hindleg venous blood just before stopping the infusion were 15.2 and 3.4 mEq/L, respectively. Final pressures obtained 5 min. after stopping infusion. Entire sequence completed within 20 min. See text for responses to vasoactive substances.

during and after infusion of 0.8 ml./min. calcium chloride into the brachial artery. The hematocrit did not change. Seven animals were studied in order to find the range of infusion rates which significantly raised calcium concentration in the leg without measurably affecting concentrations in the body. Infusion rates of 0.1 to 2.3 ml./min. were explored. It was found that rates up to 0.33 ml./min. raised cephalic venous concentrations over a range which occurs naturally without affecting the level in the body for about 15 min. This allowed sufficient time for measurement of pressures, withdrawal of blood samples, and injection of vasoactive substances. In the next 10 animals, 10 per cent calcium chloride was infused into the brachial artery at 0.1 and 0.33 ml./min. The effects upon pressures, resistances, responses, and cation concentrations are presented in table 2. Calcium concentration in cephalic venous serum rose without significant changes of sodium and potassium concentrations. Associated with this was an increase of arterial pressures which sometimes persisted as long as 30 min. after stopping the infusion. These pressure rises resulted mainly from elevation of small vessel resistance but also from a small rise of arterial resistance in 7 of 10 animals. The levarterenol response decreased in 8 of 9 tests. Like arterial pressures, levarterenol responses did not return to control values 5 min. after stopping the infusion. The methacholine response was unaffected. Aortic pressure increased slightly towards the end of the infusion in 4 of 5 animals in which it was measured.

Magnesium (24 animals)
Ten per cent magnesium sulfate was infused into the brachial arteries of 15 animals at rates ranging between 0.3 and 2.3 ml./min. Brachial and small arterial pressures regularly decreased as a function of the infusion rate, and promptly returned toward control levels upon stopping the infusion. In 6 animals, the infusion rates were 0.3, 0.6, and 1.0 ml./min. in that order. Results obtained from these animals are presented in table 3. Total resistance decreased mainly because of fall of small vessel resistance. Arterial and venous resistances also decreased slightly. Measurements of the serum levels of magnesium and calcium in cephalic and hindleg venous blood in 3 animals indicated that infusion rates up to 0.33 ml./min. allowed adequate time for detailed studies before the magnesium level became greatly elevated in the body. Therefore, 10 per cent magnesium sulfate was infused into the brachial artery of 9 animals at rates of 0.10 and 0.33 ml./min. Pressure, resistance, and cation concentration changes are present.

*Magnesium concentration also did not change in the one animal in which it was measured.

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CATIONS AND BLOOD VESSELS

Figure 2

Relation of serum sodium concentration to responsiveness of the dog foreleg vascular bed to levarterenol and methacholine. Upper. Responses of mean brachial arterial pressure of a small dog to injections of 1 μl levarterenol into brachial artery with blood flow rate in brachial artery held constant at 45 ml/min. Serum sodium concentrations in cephalic venous blood achieved by infusing 10 per cent NaCl at 0.0, 1.0, 2.2 and 0.0 ml/min. into brachial artery. Final injection of levarterenol 5 minutes after stopping infusion. Lower. Responses of mean brachial arterial pressure of larger dog to injections of 1 μl methacholine chloride into brachial artery with blood flow rate in brachial artery held constant at 60 ml/min. Serum sodium concentrations in cephalic venous blood achieved by infusing 10 per cent NaCl at 0.0, 2.3 and 0.0 ml/min. into brachial artery. Final injection 8 min. after stopping infusion.

The higher infusion rate raised foreleg magnesium concentration to 7.1 mg./100 ml. without changing calcium concentration. Associated with this was a reduction of total resistance mainly because of a decrease of small vessel resistance. The levarterenol response decreased in each instance, whereas the methacholine response did not change significantly.

Discussion

These studies show that significant changes in the resistance to blood flow through small vessels of the dog foreleg result when serum concentrations of the major cations are locally elevated over the ranges which occur naturally. They also show that some of the cations influence vascular responses to vasoactive substances. In the following discussion an attempt will be made to show that the resistance changes result from change of the degree of contraction of arteriolar smooth muscle, that the altered responses probably result from a real change of sensitivity of the smooth muscle cell, and that the latter change may in part account for the former change.

The significance of the findings will also be discussed.

The resistance changes undoubtedly result from change of the calibers of vessels. Infusion of hypertonic sodium, calcium, or potassium salts produced large alterations in resistance without measurable effect upon the hematocrit. Hence the resistance changes did not result from reduction of blood viscosity because of influx of water subsequent to elevation of intravascular osmotic pressure. Further evidence in this regard is the fact that the resistance changes produced by calcium salts were opposite in direction to those produced by the salts of sodium, magnesium, and potassium. Clumping of red cells, such as has been demonstrated by Read, need not be seriously considered in these experiments. Both the concentrations and rates of administration of the solutions were considerably less than those reported to produce clumping. Further, the direction of the resistance change during infusion of the salts of sodium, magnesium, and potassium is not that predicted to result from clumping. The resistance
changes are also not related to dynamic changes of blood viscosity. Resistance commenced to change with the rate of blood flow and hence linear velocity held constant.

Most of the caliber changes result from alteration of the degree of contraction of vascular smooth muscle, rather than a passive response to change of transmural pressures or dehydration of endothelial cells. During infusion of the salts of sodium or magnesium, small vessel resistance decreased while small vessel intraluminal pressures were falling. During infusion of calcium salts, small vessel resistance increased while small vessel intraluminal pressures were rising. There is no reason to suspect significant change of extraluminal pressure. Repeated measurements of subcutaneous and muscle interstitial pressures in this preparation indicate that these pressures do not change more than a few mm. Hg until after edema can be recognized by inspection. None of the limbs became recognizable edematous in this study. Hence, the small vessel caliber changes must have resulted from change of the degree of contraction of smooth muscle because they are opposite to those predicted from change of transmural pressure. The same reasoning may be applied to the decrease of arterial caliber during infusion of calcium salts, and the increase of arterial and venous calibers during infusion of the magnesium salt. On the other hand, the small decrease of arterial caliber sometimes seen during infusion of sodium salts likely results passively. Caliber decreased as intraluminal and hence transmural pressure was falling. The caliber changes did not result from dehydration of endothelial cells because the cell fraction of the effluent blood did not change, and because the caliber change during infusion of hypertonic calcium salts was opposite to that predicted to result from dehydration.

The muscle affected in the small vessel segment is that proximal to the capillary. Before administration of magnesium sulfate (table 3), small vessel resistance averaged 1.03 mm. Hg/ml/min. Assuming that pressure in the arteriolar end of the capillary averaged 32 mm. Hg, calculated resistance for the segment from the site of the small arterial catheter to the arteriolar end of the capillary amounted to 0.73 resistance units. This leaves 0.30 units of resistance for the segment from

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### Table 2

<table>
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<tr>
<th>Infusion Rate (ml/min)</th>
<th>Calcium (mg/100 ml)</th>
<th>Sodium (mEq/l)</th>
<th>Potassium (mEq/l)</th>
<th>Brachial Artery Pressure (mm Hg)</th>
<th>Small Artery Pressure (mm Hg)</th>
<th>Cephalic Veneous Pressure (mm Hg)</th>
<th>Total Resistance (mm Hg/ml/min)</th>
<th>Arterial Resistance (mm Hg/ml/min)</th>
<th>Venous Resistance (mm Hg/ml/min)</th>
<th>Leukotaxin Response</th>
<th>Methadonan Response</th>
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</table>

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*Cephalic venous serum.

†Blood flow in brachial artery held constant at average value of 80 ml/min.

‡0.25 g of the base of levaterenal bitartrate injected into brachial artery.

§0.50 g of the salt of methacholine chloride injected into brachial artery.

**Hindleg venous serum.

***Five min. after stopping infusion.
Table 3

Average Effect of 10% MgSO₄ Infused into Brachial Artery upon Foreleg Vascular Pressures and Resistances in 6 Dogs.*

<table>
<thead>
<tr>
<th>Infusion Rate</th>
<th>Brachial Arterial Pressure</th>
<th>Small Arterial Pressure</th>
<th>Small Venous Pressure</th>
<th>Cephalic Venous Pressure</th>
<th>Total Resistance</th>
<th>Arterial Resistance</th>
<th>Small Vessel Resistance</th>
<th>Venous Resistance</th>
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<tr>
<td>mL/min.</td>
<td>mm. Hg</td>
<td>mm. Hg</td>
<td>mm. Hg</td>
<td>mm. Hg</td>
<td>mm. Hg/ml/min.</td>
<td>mm. Hg/ml/min.</td>
<td>mm. Hg/ml/min.</td>
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*Brachial arterial blood flow held constant at average value of 75 ml./min.
†Just before starting infusion.
‡Five minutes after stopping infusion.

the arteriolar end of the capillary to the site of the small venous catheter. Magnesium sulfate decreased small vessel resistance by 0.43 units. This decrease exceeds the absolute level of resistance offered by capillaries and veins before infusion of magnesium sulfate. Hence, most of the resistance change necessarily occurred in the arteriole-containing segment proximal to the capillary. Calculations using the data obtained during infusion of other cations yield similar results.

The muscular effects result from the cation portion of the salts. Resistance decreased during infusion of 4 different sodium salts. Resistance increased during administration of 3 different calcium salts. Five potassium salts decreased resistance. Hence, the effects are characteristic of the cations rather than the anions.

The muscular effects demonstrated by this study are the result of local actions of the cations. Remote actions were not involved in the responses because the resistance changes appeared immediately upon starting the infusions into the artery and were well established long before cation levels were measurably elevated in the body. These cations may not have remote actions which effectively antagonize their local actions. In some of the experiments, the rate of infusion into the brachial artery was sufficiently rapid and prolonged to slightly increase concentrations in the body. Nevertheless, foreleg resistance remained low during sodium and magnesium infusions and high during calcium infusions. Aortic pressure decreased slightly during infusion of magnesium and increased slightly during infusion of calcium. Subsequent experiments show that both aortic pressure and foreleg resistance fall following intravenous injection of large amounts of hypertonic sodium chloride solution. The literature indicates that arterial pressure may fall following intravenous injection of hypertonic magnesium sulfate, whereas it may rise in association with intravenous injection of hypertonic solutions of calcium salts, vitamin D intoxication, idiopathic hypercalcemia, and hyperparathyroidism. By contrast, potassium and hydrogen have remote actions which may effectively antagonize their local actions. Hence, total foreleg resistance falls when potassium salts are infused into the brachial artery at a low rate, but then rises above the control value when the infusion rate is elevated so as to increase serum concentrations in the body. The fall in resistance results from decrease of small vessel resistance and the rise from increase of arterial resistance. The latter may be prevented by adrenergic blockade. Many studies indicate that intravenous injection of potassium chloride results in an adrenal discharge. Hence this remote action of potassium, operating on the
Table 4
Average Effect of 10% MgSO₄ Infused into Brachial Artery upon Aortic Pressure, Foreleg Vascular Pressures, Resistances, Responsiveness and Cation Concentrations* in 9 Dogs.†

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<tr>
<th>Sodium Rate (ml/min)</th>
<th>Magnesium (mg/L/100 ml)</th>
<th>Calcium (mg/L/100 ml)</th>
<th>Aortic Pressure (mm Hg)</th>
<th>Pulmonary Artery Pressure (mm Hg)</th>
<th>Small Artery Pressure (mm Hg)</th>
<th>Venous Pressure (mm Hg)</th>
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<th>Metabolism Serum</th>
<th>Total Resistance (mm Hg/ml/min.)</th>
<th>Arterial Resistance (mm Hg/ml/min.)</th>
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<td>9.4</td>
<td>136</td>
<td>131</td>
<td>97</td>
<td>10</td>
<td>1</td>
<td>**</td>
<td>1.63</td>
<td>0.40</td>
<td>1.12</td>
<td>0.11</td>
<td>0.11</td>
<td>0.11</td>
<td>2.5</td>
</tr>
<tr>
<td>0.33 (2.4)**</td>
<td>7.1</td>
<td>9.4</td>
<td>136</td>
<td>131</td>
<td>97</td>
<td>10</td>
<td>1</td>
<td>**</td>
<td>1.63</td>
<td>0.40</td>
<td>1.12</td>
<td>0.11</td>
<td>0.11</td>
<td>0.11</td>
<td>2.5</td>
</tr>
</tbody>
</table>

*Cephalic venous serum.
†Blood flow in brachial artery held constant at average value of 86 ml/min.
‡0.25 μg of the base of levarterenol bitartrate injected into brachial artery.
§0.50 μg of the salt of methacholine chloride injected into brachial artery.
**Hindleg venous serum.
**Five minutes after stopping infusion.

arterial segment of peripheral resistance, may account for the observation that blood pressure often rises following intravenous injection of potassium chloride despite the fact that the local action results in relaxation of arteriolar smooth muscle. Similar antagonistic actions have been observed following elevation of hydrogen ion concentration by ventilation with 20 per cent carbon dioxide.

The local actions of sodium and magnesium may result through 2 separate mechanisms. A portion of the sodium action results from some mechanism which is independent of nerves and circulating or locally released epinephrine. Sodium decreased resistance after denervation, and after denervation plus local adrenergic blockade. On the other hand, the actions of sodium and magnesium may in part be related to a real decrease in the sensitivity of arteriolar smooth muscle to epinephrine and other natural pressor substances. Both ions decreased the responsiveness of the system to levarterenol. Potassium has the same effect. The reasons for believing that the decreased responsiveness represents real rather than apparent decrease of sensitivity of smooth muscle have been presented previously. Briefly, the reasons are that a given amount of levarterenol produced the same increment in resistance in this preparation before and after dilatation by nerve section, that the responses not only decreased in amplitude but also in duration (fig. 2) and that Leonard has noted similar effects upon isolated strips of rabbit carotid artery under isometric conditions. On the other hand, the action of calcium does not appear to be related to increase of sensitivity to pressor substances. The levarterenol response was not greater during infusion of calcium. Hence this contraction likely results from some local action of calcium which is independent of this pressor substance.

Several studies suggest that these ions may have similar actions upon arterioles in other vascular beds. Katz and Lindner, using Langendorff preparations of dog hearts, noted that sodium and calcium produced an increase of coronary flow, the latter being longer in duration. Potassium in low concentrations increased flow, whereas higher concentrations...
decreased flow. Bass et al., using a similar preparation, found that magnesium chloride increased coronary flow, and altered the response to epinephrine as well. Potassium in low concentrations decreased renal vascular resistance, whereas higher concentrations increased resistance. Lowering the hydrogen ion concentration by hyperventilation increased renal vascular resistance. Most of these gross actions are similar to those in the foreleg. The different results with calcium may be related to the fact that Katz and Lindner elevated the concentration of calcium more than in the present study.

Ion effects may be involved in all activity of smooth muscle. Friedman has recently presented a theory which states that the tone of vascular smooth muscle, and hence blood pressure, depends primarily upon sodium transfer systems which govern the dynamic equilibrium between sodium entrance and ejection in vascular smooth muscle. In this theory, a transfer system is broadly defined so as to include such dissimilar agents as epinephrine, aldosterone, and pitressin. The theory was derived from observation of shift of sodium, potassium, and water and blood pressure with adrenalectomy, neurohypophyseal denervation, pitressin injection, and aldosterone injection. The present study clearly shows that Friedman's deduction regarding the action of the sodium ion upon arteriolar smooth muscle is correct. However, the study also shows that the theory is incomplete in at least 2 areas. As stated, the theory emphasizes the state of contraction of vascular smooth muscle, and ignores other well-established factors which influence blood pressure. Blood pressure is also a function of cardiac output, blood viscosity, and passive change of vessel caliber. The theory is also incomplete in regard to the state of muscle contraction because it places all of the emphasis upon the sodium ion. This and earlier studies show that the other major cations also affect the activity of vascular smooth muscle, just as they influence the activity of cardiac muscle, skeletal muscle, and nervous tissue. It may be that various agents have their characteristic actions upon vascular smooth muscle by predominantly influencing the movement of specific ions. Such an example may be serotonin and calcium. Other examples, suggested by more indirect means, are parathormone and calcium, adenyl compounds and magnesium, carbon dioxide and hydrogen, and steroids, epinephrine, acetylcholine, histamine, angiotensin and sodium and/or potassium. Examination of the segmental resistance changes observed so far (table 5) reveals that the local actions of certain natural vasomotor factors may be mimicked by elevation of the serum concentrations of the major cations. Hence, hypermagnesemia simulates the effect of acetylcholine, hypernatremia that of nerve section, and so forth. Of some interest are the facts that the actions of potassium, respiratory acidosis, and histamine are all similar, and that the serum concentration of potassium may rise during acidosis and administration of histamine. Attempts at more direct confirmation are handicapped by technical problems inherent in the determination of small changes in cation concentrations. The changes in serum concentrations likely are close to the limits of accuracy of the flame photometric method. Hence, immediately upon starting an infusion of histamine, 12 to 48 mg/min. into the brachial artery, the concentration of potassium in cephalic venous serum increased in 8 of 8 dogs. The increase ranged from 0.01 to 0.37 mEq./L. Sodium concentrations decreased 1.8 to 4.0 mEq./L in 6 but increased slightly in two. Regular changes were not observed during infusion of levarterenol or serotonin. Friedman has used another approach. He connected a glass-to-silver sodium electrode to the femoral artery of the dog, and recorded the pattern of change of plasma sodium concentration following the intravenous administration of pressor and depressor drugs. The recorded concentration decreased following administration of levarterenol, epinephrine, and angiotensin, and appeared to increase following acetylcholine, histamine, and isopropylnorepinephrine.
Table 5

Local and Remote Actions of Some Important Factors Upon Total and Segmental Vascular Resistances in the Dog Limb.

<table>
<thead>
<tr>
<th>Factor</th>
<th>Total Resistance</th>
<th>Small Vessel Resistance</th>
<th>Arterial Resistance</th>
<th>Venous Resistance</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Local</td>
<td>Remote</td>
<td>Local</td>
<td>Remote</td>
</tr>
<tr>
<td>Norepinephrine</td>
<td>↑</td>
<td>↓</td>
<td>↑</td>
<td>↓</td>
</tr>
<tr>
<td>Acetylcholine</td>
<td>↓</td>
<td>↑</td>
<td>↓</td>
<td>↑</td>
</tr>
<tr>
<td>Epinephrine</td>
<td>↑</td>
<td>↓</td>
<td>↑</td>
<td>↓</td>
</tr>
<tr>
<td>Serotonin</td>
<td>↑</td>
<td>↓</td>
<td>↑</td>
<td>↓</td>
</tr>
<tr>
<td>Histamine</td>
<td>↓</td>
<td>↑</td>
<td>↓</td>
<td>↑</td>
</tr>
<tr>
<td>Pituitrin</td>
<td>↑</td>
<td>↓</td>
<td>↑</td>
<td>↓</td>
</tr>
<tr>
<td>Pitocin</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
<td>-</td>
</tr>
<tr>
<td>Angiotensin</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
</tr>
<tr>
<td>Nerve section</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
<td>-</td>
</tr>
<tr>
<td>Adrenergic blockade</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
<td>-</td>
</tr>
<tr>
<td>Nerve stimulation</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
</tr>
<tr>
<td>Vagotomy</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
</tr>
<tr>
<td>Cold</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
</tr>
<tr>
<td>Hypernatremia</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
<td>-</td>
</tr>
<tr>
<td>Hyperkalemia</td>
<td>↓</td>
<td>↑</td>
<td>↓</td>
<td>-</td>
</tr>
<tr>
<td>Hypercalcemia</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
</tr>
<tr>
<td>Hypermagnesemia</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
<td>-</td>
</tr>
<tr>
<td>Respiratory acidosis</td>
<td>↓</td>
<td>↑</td>
<td>↓</td>
<td>-</td>
</tr>
<tr>
<td>Respiratory alkalosis</td>
<td>↑</td>
<td>↑</td>
<td>↓</td>
<td>-</td>
</tr>
<tr>
<td>Hypomagnesia</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
</tr>
</tbody>
</table>

Absence of an arrow indicates that the particular action has not been systematically tested.
↑ indicates increase of resistance.
↓ indicates decrease of resistance.
* indicates no change of resistance.

The apparent discrepancy in the direction of the change of sodium concentration between local and systemic administration may be related to the fact that systemic administration of histamine is followed by an adrenal discharge. That a given agent may act through more than one ion is suggested by the facts that histamine and the steroids produce reciprocal changes in the serum concentrations of sodium and potassium, and that administration of one cation depresses the concentration of the other (fig. 1). In view of the above, a more all inclusive restatement of Friedman's theory might be that the state of contraction of vascular smooth muscle is a function of the concentrations of the major cations, and perhaps anions, within and without the cell, and hence of anything that affects these concentrations, and that other blood pressure controlling factors remaining unchanged, this state of contraction will produce appropriate effects upon blood pressure.

These studies are important because of their possible relationship to the control of blood flow and blood pressure. It is clear that local manipulation of the serum concentrations of the major cations results in large changes in the resistances to blood flow through the foreleg and kidney of the dog. Since there are many possible ways in which the local concentrations of the cations may change this finding suggests that these ions may be important factors in the regulation of flow through these tissues. Local elevation of the serum hydrogen, sodium, magnesium, or potassium concentration would be expected to increase the rate of blood flow, and local elevation of calcium concentration would be expected to decrease the rate of blood flow. Simultaneous change of the concentrations of several cations may produce greater effects than change of the concentration of only one cation. Blood
CATIONS AND BLOOD VESSELS

pressure will be affected following change of concentration in the entire body if the local actions are similar in other beds, if the local actions are not antagonized by remote actions, and if cardiac output does not change in an opposite direction.

Many observations in animals and man indicate a relationship between the major cations and the level of arterial pressure. Pressures in animals change when intake is increased or decreased, distribution is altered, or excretion is increased or decreased. A few examples are oral or parenteral administration of cation salts, respiratory acidosis or alkalosis, intraperitoneal injection of 5 per cent glucose solution, adrenalectomy, nephrectomy, and administration of steroids. Associated with the blood pressure changes may be alteration of the concentrations of cations in the walls of large arteries, and altered blood pressure response to vasoactive substances. Similar relationships have been observed in humans. Some studies indicate a positive correlation between salt intake and the incidence of essential hypertension. Abnormal blood pressure levels are frequently observed in conditions which alter distribution and excretion of cations. These conditions include hypophysial, adrenal, parathyroid and renal disease, eclampsia, vomiting, diarrhea, and excessive administration of ACTH and steroids. Essential hypertensives may also have abnormal excretion and distribution. They excrete a load of sodium at an accelerated rate and may have low serum levels of magnesium and potassium. As in animals, abnormal concentrations of cations and water have been observed in the walls of large arteries, and essential, steroid, renal, and eclamptic hypertensives respond abnormally to pressor and depressor substances. Of particular interest is the fact that the blood pressure level may be returned to normal by decreasing or increasing cation intake, decreasing or increasing cation excretion, or repair of the cation distribution defect. Examples are sodium restriction for various types of hypertension, saline for the hypotension of Addison’s dis-

ease, correction of vomiting and diarrhea for the hypotension of gastrointestinal diseases, and, most important of all, potent diuretics for various types of hypertension. These relationships between cations and blood pressure, viewed in the light of the present findings, suggest that abnormalities of the concentrations of the 5 major cations might well explain many hypertensive and hypotensive states. This possibility has been considered in more detail in a previous communication.

Summary

Various salts of sodium, calcium, and magnesium were infused into the brachial artery of the dog at rates which raised serum cation concentrations in the leg without significantly affecting concentrations in the body. Pressures were measured at 4 sites along the length of the foreleg vascular bed while the rate of blood flow in the brachial artery was held constant. Changes of arterial, small vessel, and venous calibers were inferred from calculations of resistance. Responsiveness of the vessels was assessed by injecting levartrenol and methacholine into the brachial artery.

Total resistance and the responses to the vasoactive agents progressively decreased as a function of sodium or magnesium concentrations. The resistance decreases resulted mainly from decrease of small vessel resistance. The actions of sodium remained following local denervation and adrenergic blockade. Total resistance increased as a function of calcium concentration. The resistance increase resulted mainly from increase of small vessel resistance.

These findings indicate that local sodium or magnesium excess causes dilatation of the arterioles in the dog foreleg, whereas calcium excess causes constriction. The sodium dilatation results from some action upon vascular smooth muscle which is independent of nerves and circulating or locally released adrenalin, as well as from decreased responsiveness of smooth muscle to vasoactive substances. Changes of responsiveness also appear to be involved in the magnesium dilatation, but not in the calcium constriction.
These findings have been discussed in relation to regulation of blood flow and pressure.

Acknowledgment

The technical assistance of Clarice Bull, Booker Swindall, James Grisam and Roger Hurwitz is gratefully acknowledged.

Summario in Interlingua

Varie ales de natrium, calcium, o magnesium esseva infusionate in le artery bracliial del can a velocitates que augmentava le concentrationes cationic del serum in le gamba sin offer significativeniente ille concentrationes in le corpore. Le tension de sanguine in le gamba sin afficer significativeniente ille esseva infusionate in le artery brachial del can a volocitates que augmentava le concentrationes cationic in le artery bracliial esseva mantenite a un nivello constante. Alterationes in le calibres arterial, venos et capillaries in le lego in le arteria bracliial esseva estimate super le nivello constante. Alterationes in le calibres arterial, venos et capillaries in le lego in le arteria bracliial esseva estimate super le nivello constante. Alterationes in le calibres arterial, venos et capillaries in le lego in le arteria bracliial esseva estimate super le nivello constante. Alterationes in le calibres arterial, venos et capillaries in le lego in le arteria bracliual.

Le resistencia total e le responsivitate al agentes vasoactive declinava progressivemente como function del concentration de natrium o de magnesium. Le reductiones de resistencia resultava principalmente del redution del resistencia in le miere vessels. Le effecto de natrium promoveva post disnervation local e bloacge adrennergica. Le resistencia total esseva estimate como function del concentration de calcium. Le augmentos de resistencia resultava principalmente del augmento de resistencia in le miere vessels.

Iste constatationes indica que excessos local de natrium o de magnesium causava dilatation del arterioles in le gamba anterior del can durante que excessos de calcium causava constriction. Le dilatation per natrium promoveva post disnervation local e bloacge adrennergica. Le resistencia total esseva estimate como function del concentration de calcium. Le augmentos de resistencia resultava principalmente del augmento de resistencia in le miere vessels.

Iste constatationes es discutite in relation al regulacion del fluxo de sanguine.

References

CATIONS AND BLOOD VESSELS


changes in blood pressure and in blood sodium as measured by glass electrode. Am. J. Physiol. 196: 1049, 1959.


Local Effects of Sodium, Calcium and Magnesium Upon Small and Large Blood Vessels of the Dog Forelimb
FRANCIS J. HADDY

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