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Magnesium and the Arteries: II. Physiologic Effects of Electrolyte Abnormalities on Arterial Resistance

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DIETARY MAGNESIUM DEFICIENCY

Effects on Pressure, Flow, and Resistance

Dagirmanjian and Goldman (1970) used Sapirstein's isotope method to obtain output and organ blood flow in anesthetized rats on the 8th and 16th days of magnesium (Mg) deficiency. Blood pressure, hematocrit, organ weight, and body weight were also measured. Changes in blood flow progressed with the duration of deficiency and blood flow was differentially effected in various regions. The only changes on the 8th day were increased adenophypophyseal (anterior pituitary and median eminence) flow and decreased testicular flow. Changes were more numerous on the 16th day; blood flow as decreased in testes, epididymis, seminal vesicle, spleen, kidney, and skin, but increased in lumped gut and liver. Adenohypophyseal flow was now normal, as were blood pressure, cardiac output, and hematocrit. Thus, it appears that resistance (pressure ÷ flow) increases in many organs as the deficiency progresses, but this occurrence is balanced by decreased resistance in the large splanchnic area, resulting in unchanged total peripheral resistance. It is noteworthy that lumped skin blood flow was not increased on the 8th day, when the nose, ears, and footpads were obviously erythematous, and actually decreased on the 16th day, when the erythema was gone.

A few animals survived 40 days. At this time, flow was markedly reduced in most organs, averaging 50%. The exceptions were anterior and posterior pituitary, thymus, liver, lung, heart, and carcass where the reductions were only about 20%. In contrast, intestinal flow was increased 10%. Cardiac output was reduced 20%. Blood pressure and hematocrit were not reported for the 40th day, but other studies indicate that they are both reduced by this time (Cantin, 1970; Itokawa et al., 1974a).

Mechanism of Increased Resistance

Multiple factors appear to contribute to the increase in resistance seen in most organs. As indicated in Part I, dietary Mg deficiency can produced hypomagnesemia, hypokalemia, hypercalcemia (in the rat), increased renin and aldosterone secretion, degeneration and edema of the

blood vessel wall, platelet and erythrocyte membrane abnormalities, and effects on coagulation factors. Increased serotonin blood levels have also been described. Most of these changes can increase resistance in test systems through active or passive constriction or increased blood viscosity.

Active constriction Magnesium: Little is known about the regulation of intracellular (i.c.) free magnesium ion (Mg^{++}) concentration, but Page and Polimeni (1972) have suggested that in myocardium it is maintained at a concentration lower than that of the extracellular (e.c.) compartment by an active, energy-requiring process. Palatý (1971, 1974) has proposed the same for the vascular smooth muscle cell.

More is known about its role in contraction. In heart, Mg can displace calcium (Ca) bound to the cell surface, thereby inhibiting Ca influx and uncoupling excitation from contraction (Langer et al., 1974; Shine and Douglas, 1974). Lanthanum (La) is the potent example of cation uncoupling agents, such as manganese (Mn), cadmium (Cd), nickel (Ni), zinc (Zn), and Mg (Langer et al., 1974). Mole for mole, Mg is 20 times weaker as an uncoupler than is La. (The ability of a cation to displace surface-bound Ca depends on the size of its nonhydrated radius; the closer its radius is to that of Ca, the more Ca it displaces. The radius of La is the same as that of Ca, while Mg is much smaller.) Nevertheless, Mg can greatly depress contractile force by this mechanism, if its e.c. concentration is raised sufficiently (Shine and Douglas, 1974).

Similar studies are not available for vascular smooth muscle, but it has been suggested that here, too, cations compete with each other for surface binding sites (Altura and Altura, 1971; Jurevics and Carrier, 1973; Turlapaty and Carrier, 1973; Altura and Altura, 1974). In visceral smooth muscle, these superficial sites have been localized to the surface of the plasma membrane (Wolowyk, 1971). Among the common cations, binding affinity is greatest for Ca and Mg, next in line is potassium (K) and least is sodium (Na) (Goodford and Wolowyk, 1971). However, considering e.c. concentrations of these cations, one would predict that most of the sites are normally occupied by Na and Ca. Magnesium competes with Ca for the binding sites and, therefore, as might be predicted, increased e.c. Mg concentration lowers the tissue Ca content (Goodford, 1967). If a similar competition exists in vascular smooth muscle, decreased e.c. Mg concentration should raise tissue Ca content. This has in fact been found to be the case (Altura and Altura, 1971; Palatý, 1971). It is tempting to speculate that the reciprocal changes in serum and tissue Ca sometimes seen on lowering or raising serum Mg concentration by dietary means (see Part I) result in part via this mechanism.

The activity of cell membrane Na/K ATPase, the enzyme which provides energy for active Na and K transport by splitting ATP, is dependent upon Mg. Erythrocyte membrane ATPase activity decreases with the Mg concentration in the incubating medium (Welt, 1964). Prolonged exposure of rat diaphragm (Whang and Welt, 1963) and blood vessels (Palatý, 1971) to Mg-free solutions results in loss of K and gain of Na, suggesting a reduced efficiency of operation of the Na/K ATPase-activated electrolyte pump. In vascular smooth muscle, this pump is electrogenic; increased speed of pumping hyperpolarizes the membrane, while decreased speed of pumping does the reverse (Anderson, 1976). This suggests the possibility that Mg-free solutions eventually depolarize the membrane, thereby increasing Ca permeability and, consequently, Ca influx. As

pointed out above, exposure of blood vessels to reduced Mg concentration does, in fact, increase the tissue Ca content.

Magnesium may also influence certain i.c. reactions of importance to the contractile process. Recent studies in skeletal muscle (Potter and Gergeley, 1975) show the existence of six divalent cation binding sites on troponin C (the Ca-sensitive regulatory protein associated with the thin actin-containing filament): two high affinity Ca^{2+} binding sites that also bind Mg^{2+} competitively (Ca^{2+} -Mg^{2+} sites); two sites with lower affinity for Ca^{2+}that do not bind Mg^{2+} (Ca^{2+} -specific sites); and two sites that bind Mg^{2+} and not Ca^{2+} (Mg^{2+} -specific sites). Studies on myofibrillar ATPase show that only the two Ca^{2+} - specific sites are involved in regulating the ATPase. Recent evidence suggests that, in smooth muscle, the calcium-binding regulatory protein is associated with myosin rather than with actin, as in striated muscle (Murphy, 1976). Attempts to detect troponin have thus far failed. The significance of this difference is not clear, but if this Ca-binding regulatory protein has Ca^{2+} - Mg^{2+} binding sites which regulate the ATPase, changes in i.c. Mg^{2+} concentration could influence contractility by allowing more or less binding of Ca^{2+}. In any event, the functional responses to changes in Ca concentration are much the same in the two types of muscle; the binding of Ca to the regulatory protein allows actin to form a complex with myosin which, in the presence of Mg, has a high ATPase activity. The result is increased ATP breakdown, liberation of energy, and shortening. It would also be interesting to know whether, in the cell, the myofibrillar ATPase activity is sensitive to the Mg concentration. Finally, the Ca ATPase in sarcoplasmic reticulum, which appears to be important for the active transport of Ca from the sarcoplasm into the sarcoplasmic reticulum, is also Mg dependent. Thus, changes in i.c. free Mg concentration might also influence relaxation (Fabiato and Fabiato, 1975).

Clearly, Mg has the potential for directly influencing contractile activity at several cellular levels, among which are the cell surface, the filaments, and the sarcoplasmic reticulum.

It is well established that increased e.c. Mg concentration produces almost immediate relaxation of vascular smooth muscle by a direct effect. Intra-arterial infusion of Mg produces a rapid fall in vascular resistance in a variety of vascular beds (Haddy, 1960; Overbeck et al., 1961; Haddy and Scott, 1965; Scott et al., 1968; Overbeck et al., 1969). The effect on flow is particularly impressive in the gastrointestinal tract, because the visceral smooth muscle also relaxes, thereby removing compression from the blood vessels (Chou et al., 1963; Dabney et al., 1967; Haddy et al., 1967). The rapidity of the response and the apparent insensitivity of i.c. free Mg concentration in vascular smooth muscle to changes in e.c. concentration (Palaty, 1971, 1974), suggests an action at the cell surface. Perhaps the Mg displaces Ca from superficial anionic binding sites, reducing the available Ca^{2+} for entrance with each depolarization at the small artery and arteriolar levels. Perhaps it also hyperpolarizes the membrane (by stimulating the electrogenic pump?), resulting in fewer depolarizations. Hyperpolarization has been reported in a tumor cell (Smith et al., 1972). It is also possible that part of the response results from decreased responsiveness to circulating catecholamines; during the infusion of Mg at a rate which barely affects resistance, the response to injected catecholamines is substantially reduced (Haddy, 1960; Frohlich et al., 1962).

Since hypermagnesemia causes vasodilation by a direct mechanism, one may ask whether the hypomagnesemia seen in dietary Mg deficiency contributes, per se, to the increase in arterial resistance. Studies of hy-

pomagnesemia in intact vascular beds of the dog have been negative for time periods ranging from 5 to 10 min (Haddy et al., 1963; Anderson et al., 1972). For example, reduction of the Mg concentration in the arterial blood perfusing the gracilis muscle for 10 min by dialysis of the entering arterial blood against a Mg-free Ringer's solution has no effect on resistance to flow through the gracilis muscle (Anderson et al., 1972). Studies in isolated vessels, however, have been positive. Isolated rabbit aortic strips have been exposed to Mg^{2+}-free Krebs-Ringer solution for 60 min and about a quarter of them respond with a slow 10 to 50% increase in tension (Altura and Altura, 1971). Furthermore, the rat aortic strip responds immediately and regularly to reduction of Mg concentration; the greater the reduction in Mg concentration the greater the magnitude of the mechanical response (Altura and Altura, 1974). In fact, exposure of the strips to a Mg^{2+}-free solution can result in contractions which exceed 50% of the epinephrine-induced maximal response. The response is dependent on the Ca concentration, but is not influenced by adrenergic, cholinergic, serotonergic, or histaminergic antagonists.

It seems unlikely that these immediate responses could result from a fall in the i.c. concentration of Mg. The arterial smooth muscle cell (Somlyo et al., 1966; Wallach et al., 1967; Altura and Altura, 1970; Palatý, 1971), like the heart cell (Page, 1971; Page and Polimeni, 1972), does not readily release its Mg. Intracellular content seems to be quite insensitive to reduced e.c. levels. The release of tissue Mg during incubation in Mg-free solutions consists of fast and slow components. The former, lasting less than 1 hr, represents only about 25% of the total tissue Mg. After 24 hr, the tissue still contains half of the original amount. It is believed that the easily exchangeable fraction comes from e.c. fluid and superficial anionic binding sites (e.c. protein-polysaccharides and the cell membrane). Calcium content rises (Altura and Altura, 1971; Palaty, 1971) very likely in part because this ion now occupies the superficial binding sites vacated by Mg. This could account for the immediate contraction, since now more Ca would be available for entrance. The slow component of release is probably of i.c. origin. If so, reduced i.c. concentration could eventually participate in the contraction of these isolated vessels (as suggested by others (Jurevics and Carrier, 1973; Altura and Altura, 1974) by effects at the various i.c. sites outlined above. (In dietary Mg deficiency, however, a fall in the Mg content of tissue is not always seen (Martindale and Heaton, 1964; Dagirmanjian and Goldman, 1970; Hunt, 1971; Itokawa et al., 1974a,b), even at a stage when the serum level of Mg is very low; blood vessel Mg content appears not to have been measured during dietary deficiency). Finally, as pointed out above, there is evidence that prolonged exposure to Mg-free solutions slows the Na/K pump. Slowing the pump by other means leads to depolarization because the pump is electrogenic. Thus, it is possible that depolarization also eventually contributes to the contraction of these isolated vessels.

Potassium: Animals (rat, dog) with dietary K deficiency have many of the features of those with dietary Mg deficiency. They gain weight slowly and eventually become hypotensive. The hypotension results from a decrease in cardiac output; peripheral resistance is elevated (Abbrecht, 1972). They have increased renal vascular resistance, decreased renal blood flow, and increased plasma renin activity. The latter tends to disappear with time, concurrent with Na retention. Potassium content

decreases and Na content increases in skeletal muscle and cardiac muscle. Focal myocardial necrosis has also been described, and the contractility of papillary muscle, isolated from the heart, is depressed.

The increased total peripheral resistance cannot be explained by increased sympathetic outflow, since it appears to not be influenced by ganglionic blockade (Abbrecht, 1972). Neither can it be explained by the renin-angiotensin system, since renin, after an initial increase, returns toward normal while resistance continues to increase. It seems more likely that it is related to a direct effect of hypokalemia on the vascular smooth muscle.

Acute local hypokalemia produces a rise in resistance in most vascular beds (Haddy et al., 1963; Anderson et al., 1972; Chen et al., 1972; Brace, 1974; Brace et al., 1974; Haddy, 1975). Figure 1 shows the time course of the response in the dog forelimb (Brace, 1974). Reduction of the K concentration to 2.3 meq/liter (by dialysis of the entering arterial blood against a K-free Ringer's solution) produces a rather prompt rise in perfusion pressure at constant flow which tends to wane somewhat with time. The response quickly disappears when the K concentration is returned to normal.

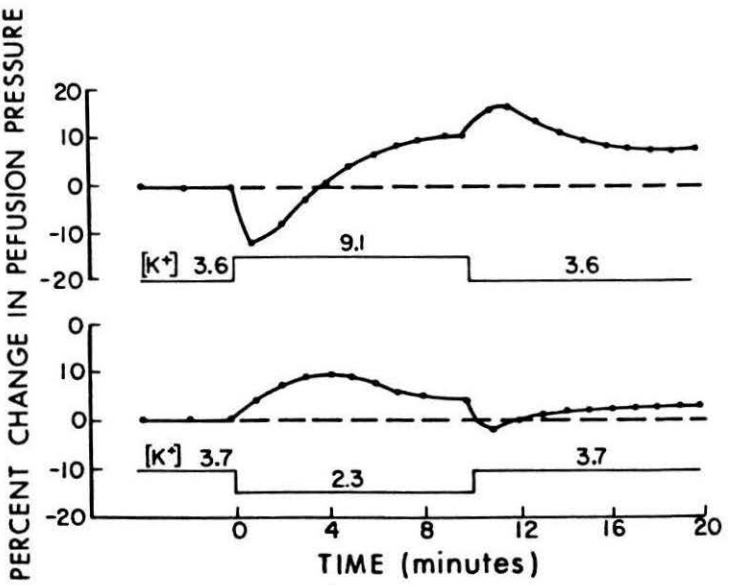

Figure 1. Time course of the response of perfusion pressure at constant flow in a dog forelimb to reduction in K concentration in the perfusing blood (lower panel). Hypokalemia produced by dialyzing the entering arterial blood against a K-free Ringer's solution (from Brace, 1974).

Figure 2 shows that the response also occurs in the canine coronary vascular bed and that this response is associated with a large increase in myocardial contractile force (Brace et al., 1974).

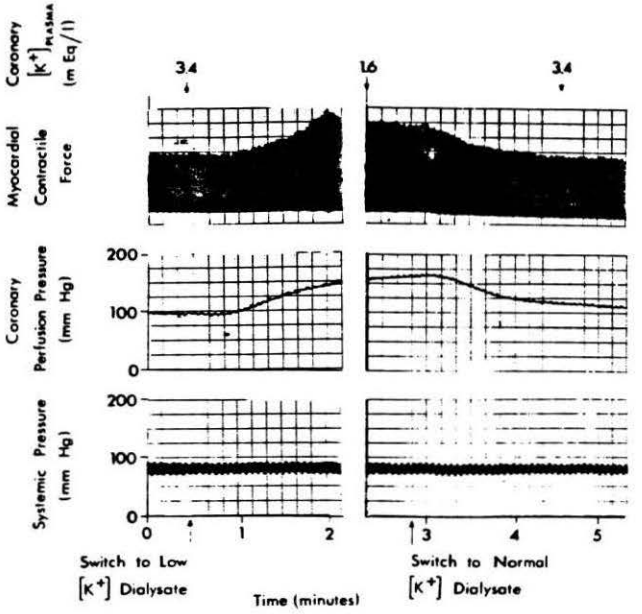

Figure 2. Typical responses of canine coronary perfusion pressure (at constant flow) and left ventricular contractile force to hypokalemic perfusion of the coronary vascular bed (from Brace et al., 1974).

Figure 3 shows the magnitude of the steady state response (after about 7 min) in canine gracilis muscle (Anderson et al., 1972). Here, percent change in perfusion pressure is plotted as a function of the percent change in K concentration in the entering blood. The response is linear, perfusion pressure rising about 5% for each 20% reduction in K concentration. It is also apparent from the figure, that hypomagnesemia has no acute direct effect on the reistance to flow through this preparation. Reduction of Mg concentration by 80% for about 7 min fails to affect resistance, either in the absence or presence of hypokalemia.

Hypokalemic vasoconstriction is apparently related to Na/K ATPase, because it can be abolished by administration of ouabain, a potent Na/K ATPase inhibitor. Figure 4 shows the response of gracilis perfusion pressure at constant flow to hypokalemia before and after the administration of ouabain (Chen et al., 1972). Perfusion pressure rises before, but not after, the administration of ouabain. Figure 5 shows that this can also be demonstrated in isolated arterial strips (Gebert and

Piechowiak, 1974). In fact, here ouabain can actually reverse the response.

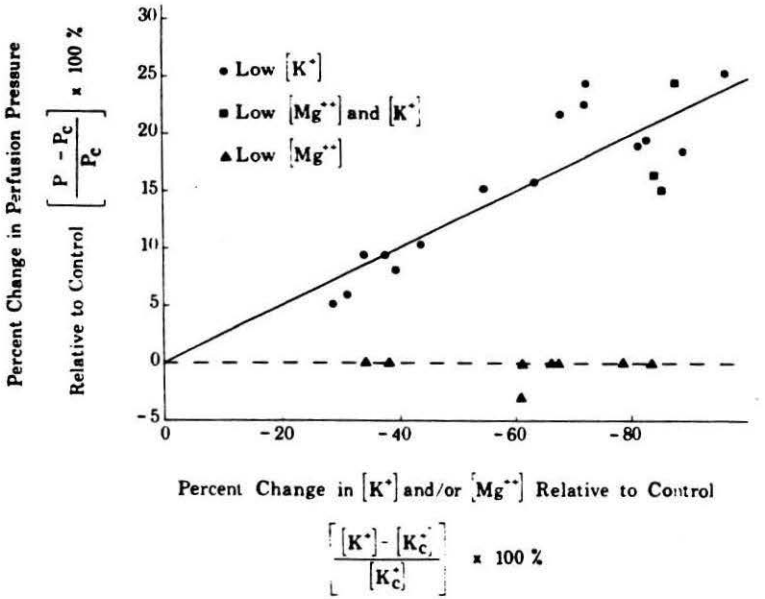

Figure 3. Steady state responses of the canine gracilis vascular bed to hypokalemic, hypomagnesemic, and hypokalemic-hypomagnesemic perfusion. Perfusion pressure was measured at constant flow about 7 min after establishing the concentration change in the perfusing blood with a dialyzer interposed in the perfusion line. In the case of hypokalemic-hypomagnesemic perfusion (■), data are plotted with percent change of K on the abscissa (from Anderson et al., 1972).

There is now good evidence that hypokalemia depolarizes the vascular smooth muscle cell. Figure 6 shows computed and measured membrane potential as a function of the external K concentration and it is apparent that the cell potential decreases as the K concentration is reduced below the normal value (Brace et al., 1974; Anderson, 1976). Figure 7 shows the time course of the measured response in isolated perfused rabbit ear artery (Hendrickx and Casteels, 1974; Anderson, 1976).

From data such as these,-we proposed that hypokalemia constricts arterioles by decreasing the activity of the Na/K ATPase in the sarcolemma of the smooth muscle cell, thereby suppressing an electrogenic Na/K pump, resulting in depolarization (Chen et al., 1972). An ATPase which is sensitive to Na + K and inhibited by ouabain has been isolated from blood vessel membranes (Wolowyk, 1971). Sodium/potassium ATPase has been shown to be closely linked to the Na/K pump in a variety of

cells. The Na/K pump is electrogenic (affects the membrane potential) because it transports Na and K asymmetrically; more Na^+ are pumped than K^+ (Anderson, 1976). Thus, increasing the speed of the pump, causes a loss of net positive charge from within the cell, resulting in hyperpolarization. The reverse occurs when the pump is slowed. This may, in part, explain the increase in arterial resistance seen in dietary K deficiency and also in late dietary Mg deficiency, since hypokalemia is sometimes observed at this time.

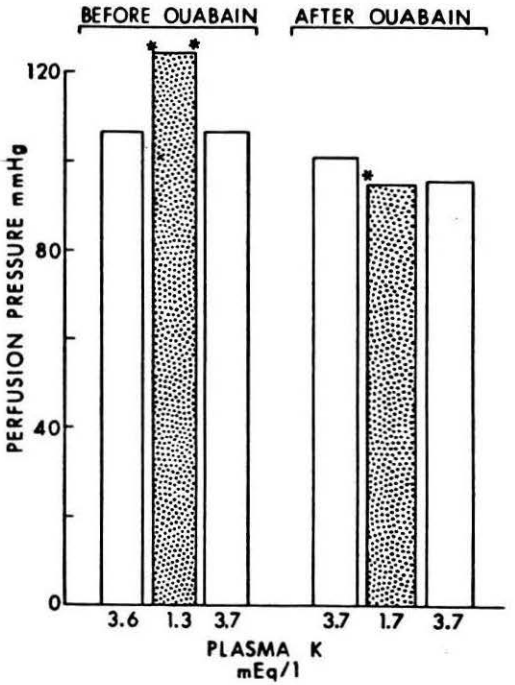

Figure 4. Effect of ouabain on hypokalemic vasoconstriction in the gracilis vascular bed of the dog. Perfusion pressure measured at constant flow while reducing the plasma K concentration in the perfusing blood with a dialyzer interposed in the perfusing line. Ouabain administered into the perfusion line. Average data presented (N=12). Average blood flow=15.8 ml/min. Stars indicate significant change from control value (from Chen et al., 1972).

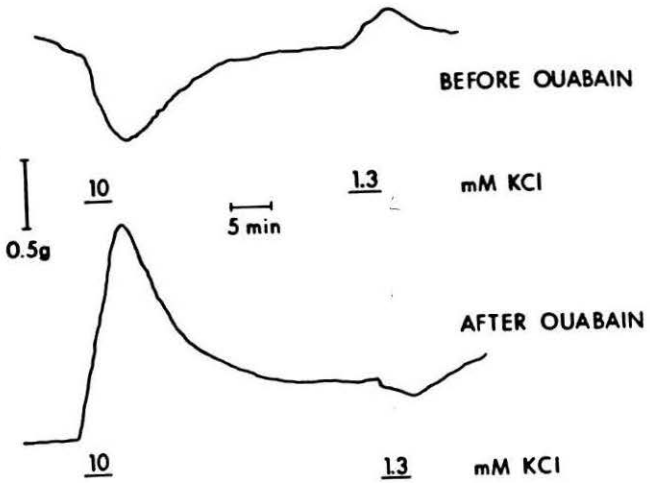

Figure 5. Effect of ouabain on the tension responses of isolated bovine facial artery to increased (10mM) and decreased (1.3mM) K concentration in the bathing fluid (from Gebert and Piechowiak, 1974).

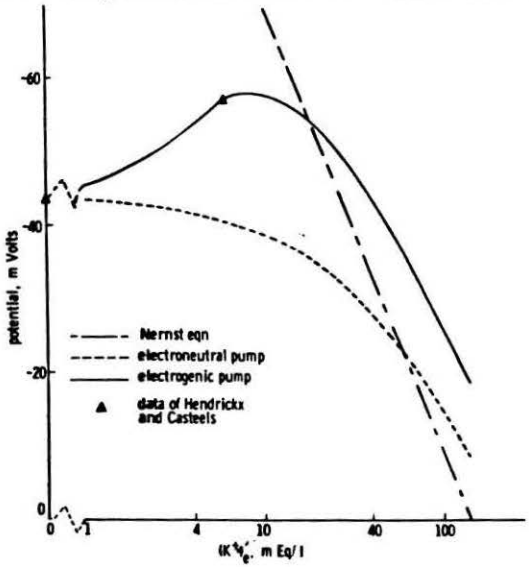

Figure 6. Computed and measured (data of Hendrickx and Casteels, 1974) membrane potential in vascular smooth muscle cell as a function of the external K concentration (from Anderson, 1976).

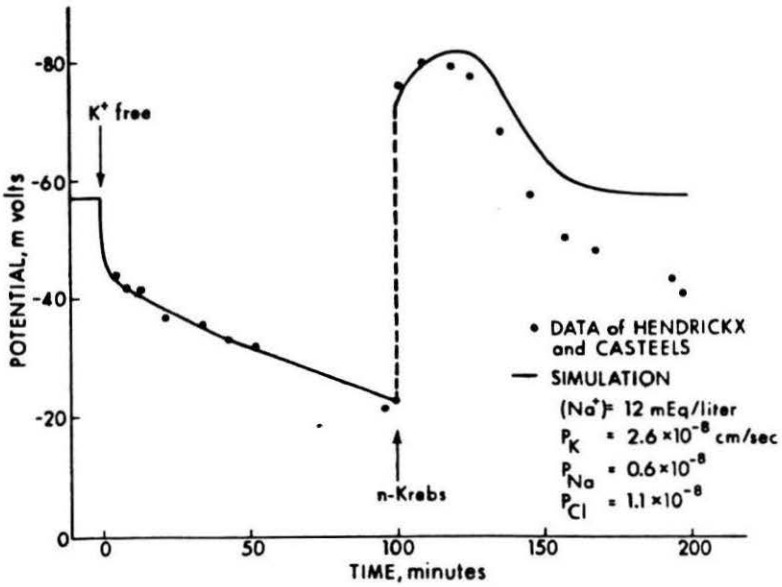

Figure 7. Time course of the change in computed and measured (data of Hendrickx and Casteels, 1974) membrane potential in the vascular smooth muscle cell of the isolated perfused rabbit ear artery on reducing the K concentration in the perfusate to zero (from Anderson, 1976).

Calcium: The direct effects of both increased and decreased e.c. Ca concentration on vascular smooth muscle will be considered, since both are seen with dietary Mg deficiency, depending upon species.

As expected, increased Ca concentration produces contraction and decreased Ca concentration produces relaxation of vascular smooth muscle in vitro (Waugh, 1962; Bohr, 1963; Hinke et al., 1964) and in situ in perfused vascular beds (Haddy, 1960; Overbeck et al., 1961; Scott et al., 1961; Frohlich et al., 1962; Haddy et al., 1963; Haddy and Scott, 1965; Scott et al., 1968). The mechanism seems to be quite straightforward. Increased e.c. Ca concentration increases the diffusion gradient for Ca, the amount of Ca bound to the sarcolemma, and possibly the store of Ca in the sarcoplasmic reticulum. Consequently, the free ionic Ca concentration in the sarcoplasm increases, particularly when the cell depolarizes. The Ca binds to the Ca binding regulatory protein associated with myosin, thereby increasing the number of interactions between actin and myosin.

The changes in the membrane potential, if anything, antagonize the responses. Increased e.c. Ca concentration stabilizes the membrane, i.e., the membrane hyperpolarizes slightly and the time between bursts of action potentials is prolonged (Axelsson et al., 1967; Riemer et al., 1973). This may, in part, account for the fact that the contraction seen on increasing the Ca concentration is frequently not great (Haddy,

1960; Bohr, 1963; Biamino and Johansson, 1970). Indeed, no effect or relaxation has been recorded in some intact vascular beds (Dabney et al., 1967; Haddy et al., 1967; Overbeck and Pamnani, 1973). On the other hand, decreased Ca concentration labilizes the membrane, i.e., it slightly depolarizes the membrane and the spike frequency at first increases (Axelsson et al., 1967; Keating, 1972; Smith et al., 1972; Riemer et al., 1973).

Thus, hypercalcemia would contribute to the increased arterial resistance seen in dietary Mg deficiency, while hypocalcemia would antagonize it (unless the hypocalcemia is the result of greater Ca binding to membranes).

Combinations: In an acute setting, combining certain electrolyte abnormalities intensifies the constriction. In dog forelimb or kidney, acute local hypokalemia, hypercalcemia, and alkalosis results in more intense constriction than occurs with any of the three abnormalities alone (Haddy et al., 1963). Furthermore, addition of hypomagnesemia to the three abnormalities produces still more intense constriction, suggesting that hypomagnesemia, while not a constrictor alone, is a constrictor in combination with certain other electrolyte abnormalities (Haddy et al., 1963).

The findings in heart are of particular interest. The changes in myocardial contractile force are often associated with an inappropriate response in the resistance to blood flow through the coronary vascular bed. The rise in force seen with acute local hypokalemia (Haddy et al., 1963; Brace et al., 1964), hyponatremia (hypoosmolality) (Brace et al., 1975), hypercalcemia (Scott et al., 1961; Haddy et al., 1963), or alkalosis (Haddy et al., 1963; Daugherty et al., 1967; Kammermeir and Rudroff, 1972) is associated with an unchanged or increased coronary vascular resistance, rather than the decreased resistance usually seen with enhanced myocardial activity. An inappropriate response is also seen when certain abnormalities are combined (Haddy et al., 1963). Thus, combining hypokalemia, hypercalcemia, alkalosis, and hypomagnesemia produces both increased force and resistance. This presents the possibility that coronary flow will not deliver enough oxygen to keep pace with utilization, thereby resulting in a fall in tissue oxygen tension, particularly if the arteries are already diseased. Coronary sinus oxygen tension has been measured in the case of hypokalemia alone and the responses are accompanied by a transient fall in oxygen tension (Brace et al., 1974).

Serotonin: Serotonin is a potent constrictor of skin arteries and veins (Daugherty et al., 1968) and produces rubor in the process. It also constricts other low resistance beds, such as those in the lung and kidney (Emanuel et al., 1959). Serotonin blood levels have been found to be elevated in the rat during dietary Mg deficiency, particularly during concurrent administration of thiamine (Itokawa et al., 1972, 1974a). Thus, it is possible that hyperserotoninemia contributes to the increased resistance seen in skin and kidney during dietary Mg deficiency (for further detail see Mechanism of Decreased Resistance).

Renin-angiotensin-aldosterone system: Angiotensin is a potent direct constrictor of blood vessels (Haddy et al., 1962). Aldosterone, on the other hand, has no demonstrable immediate direct effect on vascular re-

sistance. It does, however, slowly produce indirect effects. To an important extent, these appear to be secondary to its well known effects on the kidney. Thus, aldosterone may slowly influence vascular resistance via Na and water retention, natriuretic hormone release, increased K excretion, and alkalosis. This area has recently been reviewed in detail (Haddy, 1974).

Nervous system: Dietary Mg deficiency produces convulsive seizures and reduces Mg in brain, spinal cord, and cerebrospinal fluid in the rat (Chutkow and Grabow, 1972; Itokawa et al., 1974a). Elevation of the concentration of Mg^{2+} has long been recognized as an effective method of prevention of transmission at virtually all chemical synapses (Rubin, 1970; Wood, 1975). There is some evidence that Mg facilitates norepinephrine uptake by adrenergic nerve granules (Von Euler and Lishajko, 1973). Thus, it is possible that the reduced Mg concentration increases vascular resistance, in part, by decreasing uptake of norepinephrine into central and peripheral nerve endings, resulting in higher concentrations of neurotransmitter at the effector.

A preliminary study suggests that dietary Mg deficiency reduces blood volume (El Shahawy, 1971). If true, this would reduce cardiac output and blood pressure and reflexively increase vascular resistance via the baroreceptors and vasoconstrictor nerves.

Passive constriction As indicated in Part I, prolonged dietary deficiency of Mg produces vascular degenerative changes in various organs, particularly the heart. This disorganization of the vessel wall leads to a passive reduction in the caliber of the lumen, thereby contributing to the increased resistance. If thrombi or platelet aggregates form, resistance would increase via the same mechanism.

Increased blood viscosity? Decreased hematocrit, due to a decreased number of red cells per unit volume, has been reported in Mg-deficient rats (Whang and Welt, 1963; Elin et al., 1971a,b). This by itself would tend to reduce blood viscosity. However, the red cells are large and spherocytic and contain reduced amounts of ATP (Elin et al., 1971b). Hence, it is possible that they are less deformable and, consequently, flow less easily through small vessels. If so, this would tend to increase resistance. Magnesium-deficient rats also develop slight hypothermia (Itokawa et al., 1974a). This would tend to raise blood viscosity and, hence, resistance.

Mechanism of Decreased Resistance

The mechanism of the decrease in arterial resistance in the adenohypophysis and lumped gut and liver is unknown, but histamine is suspect. In the rat, facial skin normally contains three times as many mast cells as abdominal skin (Belanger et al., 1957). Degranulation and pleomorphism of these cells has been observed in both areas during dietary Mg deficiency, apparently maximal on or about the 7th day (Belanger et al., 1957). By the 28th day, the number of cells is also greatly reduced in both areas (Belanger et al., 1975). Eosinophils have also been observed in sections of ear, lower lip, abdominal, scrotal and paw skin, and tongue on the 10th day; the sections also reveal large capillaries, es-

pecially in the ears (Bois, 1963). Tissue eosinophils are still present on the 20th day, although now less numerous; they are essentially absent by the 60th day (Bois, 1963). Urinary excretion of histamine is significantly elevated on the 10th day, maximal on the 15th day, and normal from the 20 to 60th day (Bois, 1963). In another study, urinary histamine excretion appeared to be elevated on the 4th day, maximal on the 10th day, and near normal by the 15th day; plasma histamine concentration was increased by the 6th day and remained elevated through the 14th day (Bois et al., 1963).

The time course of these changes is roughly that of the erythema and increased adenohypophyseal blood flow. Generalized erythema (most prominent in ears, snout, paws, and scrotum and, in these areas, accompanied by slight edema) appears within a few days, is maximal on the 7 to 10th day, and then gradually disappears over the next 10 days. The increased adenohypophyseal flow is present on the 8th day and absent by the 16th day. However, the erythema is apparently not accompanied by a generalized increase in skin blood flow (Dagirmanjian and Goldman, 1970) and administration of histamine to normal rats fails to produce erythema of ears and nose, whereas administration of serotonin does (Itokawa et al., 1972, 1974b). Perhaps the changes in skin result from an interaction between histamine and serotonin. The concentration of serotonin in blood has been found to be elevated on the 28th day of a Mg-deficient, thiamine-sufficient, or thiamine excess diet (Itokawa et al., 1972, 1974a), apparently due to reduced oxidation (Itokawa, 1974b), and serotonin is well known for its ability to reduce flow and produce color changes in skin (Daugherty et al., 1968). Unfortunately, levels have not been measured earlier than the 28th day.

The time course of the changes in histamine blood concentration and urinary excretion does not fit that of the increased flow in lumped gut and liver. Here the flow is unchanged on the 8th day and elevated on the 16th and 40th days (Dagirmanjian and Goldman, 1970). Of interest, is the observation that the serotonin content of intestine is increased on the 28th day of an excess or normal thiamine, Mg-deficient diet (Itokawa, et al., 1972). Histamine content has not been measured.

It is also possible that resistance decreases in adenohypophysis and lumped gut and liver because of decreased activity of certain naturally occurring vasoconstrictor substances. It has, for example, long been known that Mg lack greatly decreases the contractile response of isolated vascular smooth muscle to neurohypophyseal hormones (Somlyo et al., 1966; Altura and Altura, 1974; Altura, 1974, 1975).

ACUTE HYPOMAGNESEMIA

In the dog, acute selective dilutional reduction in plasma Mg concentration, produced within 5 min by rapid intravenous (i.v.) infusion of a Mg-free Ringer's solution, causes a rise in blood pressure which is not seen during equally rapid infusion of Ringer's solution containing the usual amount of Mg (Emerson et al., 1970). This difference in the blood pressure response is not seen after total spinal anethesia (Mc Keag et al., 1969; McKeag, 1970) and a difference in the resistance response is not seen when the solutions are infused into the arterial supply of the limb, kidney, or heart (Haddy et al., 1963). These findings suggest that the pressor response seen in the intact animal is neurally mediated. Such studies may be relevant to blood pressure response in man during rapid i.v. fluid therapy (for shock, for example). They may also be relevant to the blood pressure changes seen in man during acute

severe hypomagnesemia iatrogenically produced by replacement of gastrointestinal and renal losses with Mg-free fluids. Here, the association of a blood pressure rise with the hypomagnesemia and of a fall to normal with Mg therapy is sometimes as striking (Hall and Joffe, 1973) as the association of hypotension and severe hypermagnesemia (Mordes et al., 1975).

On the other hand, blood pressure does not rise in the dog when the selective hypomagnesemia is produced more slowly by nondilutional techniques. For example, replacement of the fluid lost following injection of furosemide with a Mg-free Ringer's solution leads to hypomagnesemia without a change in blood pressure (Haddy and Scott, 1970, 1973). The same seems to be the case when the hypomagnesemia is produced by hemodialysis (Sellers et al., 1970; Harrison et al., 1971). This difference is unexplained. Perhaps it is in some way related to time, dilution, or degree of hypomagnesemia.

SUMMARY FOR PARTS I AND II

It is apparent from this review that Mg deficiency produces both morphological and functional changes in the arteries. These include damage to the intima, internal elastica, and media resembling infantile arteriosclerosis (particularly in the heart) and increased resistance to blood flow in most organs (exception, splanchnic vascular bed where resistance is decreased). The changes are associated with perivascular myocardial damage, decreased serum concentrations of Mg, K, and Ca, and in soft tissues, decreased content of Mg and K and increased content of Ca and Na. Increased plasma renin activity, plasma histamine concentration, blood serotonin level, and urinary aldosterone excretion have also been noted. The morphological changes are intensified and modified by nutritional factors that increase Mg requirements, such as excess vitamin D, Ca, phosphate (PO_4), and fat or by agents that mobilize bone Ca and increase Mg and K loss, such as parathyroid hormone (PTH) and the corticosteroids. Hypercalcemic agents (i.e., vitamin D) also increase the blood pressure and serum lipids. Magnesium protects against the cardiovascular damage.

The mechanism of the morphological changes in the blood vessels is not clear, but the changes almost certainly contribute to the increased arterial resistance. A contribution by vasoconstriction also seems likely. Calcium plays a central role in excitation-contraction coupling and this ion competes with Mg for binding sites on the membrane of the vascular smooth muscle cell. When e.c. Mg falls, more Ca is available on the membrane for entrance into the cell with each spike potential. Furthermore, the number of spike potentials may increase, because lack of Mg and K suppresses the Na/K pump which, because of the electrogenic nature of the pump, leads to a decrease in the resting membrane potential. Increased membrane Ca and number of spikes would elevate i.c. Ca and cause vasoconstriction. (Increased Ca binding and suppression of the Na/K pump, if generalized, would also explain hypocalcemia, increased tissue Ca and Na, and decreased tissue K; decreased Ca binding would explain the fall in tissue Ca and rise in serum Ca seen on Mg supplementation).

Increased resistance leads to decreased blood flow in most organs, since arterial pressure is normal or reduced due to decreased resistance in the splanchnic vascular bed. Decreased flow, by delivering less oxygen, may in turn play a role in the genesis of the parenchymal lesions. Increased oxygen utilization may also participate in their production,

because some of the changes seen during Mg deficiency, hypokalemia and increased tissue Ca, for example, increase myocardial activity in test systems. It is, of course, possible that the parenchymal lesions result in part from metabolic changes (at the mitochondrial level, for example), independent of oxygen tension.

When hypercalcemic agents are superimposed, Ca binding to cell membranes is increased further. This could account for the intensification of the cardiovascular calcification. It could also explain the rise in blood pressure, since increased binding should increase the contractility of both the heart and blood vessels. The role of the hypertension in the increased incidence of myocardial lesions is unclear; while the hypertension should increase oxygen utilization, it should also increase oxygen delivery, provided the lesions in the coronary vessels permit an increase in flow.

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