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The effect of magnesium deficiency and excess on bovine coronary artery tone and responses to agonists

Stanley Kalsner

Department of Pharmacology, Faculty of Health Sciences, School of Medicine, University of Ottawa, 451 Smyth Road, Ottawa, Ontario, Canada K1H 8M5

1 The hypothesis that magnesium deficiency, linked to the magnesium content of drinking water, induces major tone increases in coronary arteries and enhances their responses to vasoactive agents to an extent sufficient to explain sudden death associated with ischaemic heart disease was examined in an *in vitro* preparation.

2 The spontaneous tone of cattle coronary arteries was not increased during a 30 min exposure to Mg^{2+}-deficient Krebs until the mineral was omitted entirely from the bathing medium, and even then the observed increase was small. Only in strips maintained under extremely deficient conditions for a prolonged period, namely Mg^{2+} concentration of 0.2 mM and 0.0 mM for 3 h, was tone substantially greater than in controls in standard (1.2 mM) Mg^{2+}-Krebs.

3 Responses to acetylcholine and to noradrenaline were not increased in Mg^{2+}-free Krebs but those to potassium and to 5-hydroxytryptamine were enlarged over the lower parts of their concentration-response curves. Responses to potassium and to 5-hydroxytryptamine were also examined in Krebs containing very low concentration of Mg^{2+} (0.4 and 0.2 mM) and only modest increases in contraction size were detected. Increases in the Mg^{2+} concentration of the Krebs (to 4.8 mM) depressed responses to potassium and 5-hydroxytryptamine.

4 It is concluded that Mg^{2+} deficiency must be nearly complete (0.4–0.0 mM) to induce even moderate tone increases in coronary vessels, or to sensitize them to agonist responses, and that there is no reason to link marginally subnormal Mg^{2+} levels, occasionally reported in humans with heart disease, to marked changes in coronary dynamics.

Introduction

Several epidemiological studies have purported to demonstrate a positive association between the softness of drinking water in communities and the incidence of cardiovascular disease (Schroeder, 1960; Anderson & le Riche, 1971; Neri & Johansen, 1978; Karppanen, Pennanen & Passinen, 1978). This observation of a marked geographical variation in mortality from cardiovascular disease has been attributed, by some, to a protective effect of magnesium which is abundantly present in hard water (e.g. Anderson, Neri, Schreiber, Talbot & Zdrojewski, 1975). In support of this interpretation some workers have claimed that serum magnesium is decreased in acute ischaemic heart disease and that myocardial tissue is deficient in magnesium in victims of fatal myocardial infarction (e.g. Chipperfield & Chipperfield, 1973; Seelig & Heggtveit, 1974; Dyckner, 1980).

The involvement of magnesium deficiency in hypertension, coronary heart disease and sudden death has received considerable impetus recently with the general interest in acute coronary spasm (e.g. Kalsner, 1982) and the report that coronary artery strips maintained *in vitro*, incubated in magnesium-free Krebs, show increases in spontaneous tone, described as 'spasms' and also enhanced responses to diverse stimulants (Turlapaty & Altura, 1980). The present experiments were done to examine the likelihood that a deficiency of magnesium is instrumental in inducing major tone changes in coronary arteries sufficient to account for spasm and consequent sudden death. It appears from the work described below that a subnormal magnesium concentration is highly unlikely to explain acute coronary events or to account for any protective effect of hard water, if such indeed exists.

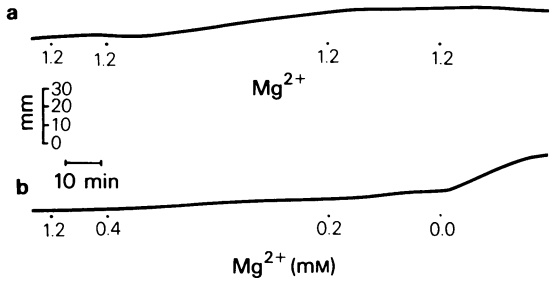

Figure 1 The effect of sequential reductions in the Mg^{2+} concentration of Krebs solution on the spontaneous tone of coronary artery strips. After initial incubation for about 120 min in standard Krebs (1.2 mM Mg^{2+}), strips were exposed as indicated (bottom trace) to Krebs containing 0.4, 0.2 and 0.0 mM Mg^{2+}. Matching strips (e.g. (a)) were maintained in standard Krebs which was replenished at the indicated points.

Methods

Cattle hearts were obtained immediately after slaughter, immersed in chilled previously oxygenated Krebs solution and transported to the laboratory (total time 20–30 min). The left descending coronary and circumflex arteries were dissected out, freed of adherent fat and cut into spiral strips of about 48 × 2.5 mm. The strips were suspended under 2 g tension in 15 ml muscle chambers at 37°C, as described previously (Kalsner, 1975); strips from both vessels were distributed equally throughout the experimental protocols, and responses to drugs were recorded isotonically on smoked kymograph paper with a magnification of 6.8 fold.

The bathing medium was Krebs-Henseleit solution (Krebs) containing (mM): NaCl 115.3, KCl 4.6, $CaCl_2$ 2.3, $MgSO_4$ 1.2, $NaHCO_3$ 22.1, KH_2PO_4 1.1 and glucose 7.8; to this medium disodium ethylenediamine-tetraacetic acid (0.03) was added to retard oxidation of amines. Special Krebs media were prepared by adjusting the concentration of $MgSO_4$ or by deleting it entirely. Physostigmine (eserine) sulphate, acetylcholine chloride, (−)-noradrenaline bitartrate, 5-hydroxytryptamine creatinine sulphate, histamine dihydrochloride, sodium nitrite, potassium chloride and propranolol hydrochloride were prepared fresh on the day of use and kept chilled in an ice bucket. Drugs were made up in 0.9% w/v NaCl solution (saline) and, in the case of amines, acidified with 0.01 N HCl.

Mean values ± s.e.mean of all data are shown.

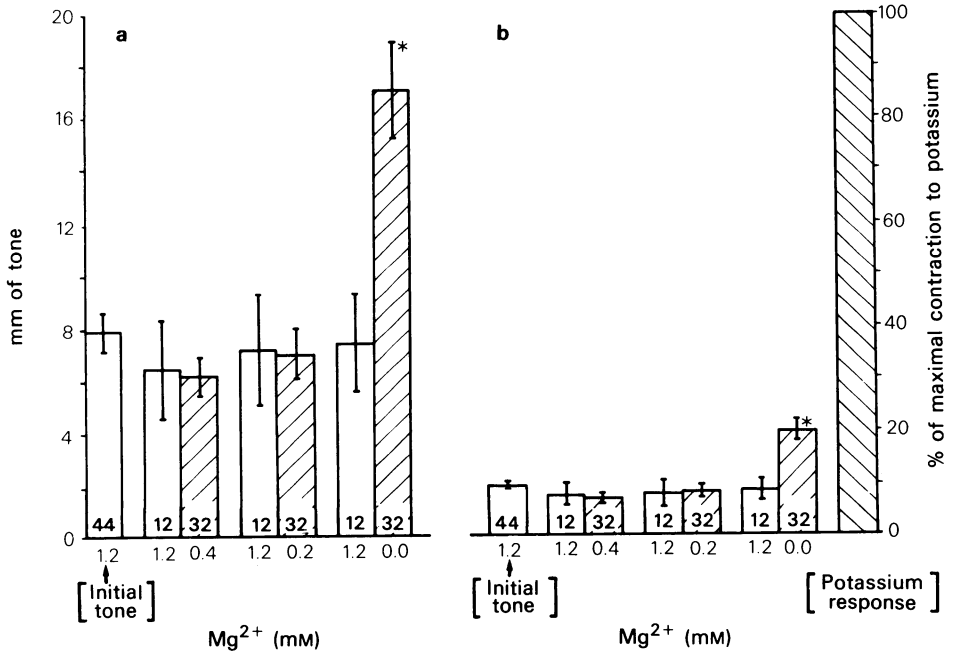

Figure 2 Effects of reductions in Mg^{2+} on spontaneous tone of coronary artery strips. The protocols were identical to those described in the text and legend to Figure 1. (a) Data expressed as mm of tone; (b) same data expressed as percentage of maximal contraction to potassium. Asterisks above treated groups (hatched columns) indicate values significantly different from matched group maintained in standard Krebs solution (1.2 mM Mg^{2+}). In this and subsequent figures, numbers of preparation are indicated within each column.

Differences with P values of 0.05 or less were considered significant. Data from concentration-response curves were generally expressed in two different ways (Kalsner, Frew & Smith, 1975), namely by calculating the mean response magnitude to individual drug concentrations (e.g. Figure 6), or by determining the average concentration which produces a particular fixed response size (e.g. Table 1). With respect to concentration-response curves, changes in response at the mean effective concentration (e.g. ED_{50}) are expressed as the ration of geometric mean values (Fleming, Westfall, De La Lande & Jellett, 1972). Each ED_{50}, or alternate value, was converted to its log and the mean for each group recorded. The antilog of each mean log is presented as the geometric mean. Due to the lack of parallelism of certain of the concentration-(dose) response curves, comparisons at alternate response levels yield somewhat different values (Kalsner, 1975).

Results

Spontaneous tone

A group of 32 coronary artery strips were equilibrated for 120 min in standard Krebs solution containing 1.2 mM Mg^{2+} and then exposed in sequence, and for the indicated times, to Krebs containing 0.4 mM Mg^{2+} (30–60 min), 0.2 mM Mg^{2+} (30 min) and 0.0 mM Mg^{2+} (30 min). A group of 12 matching strips, taken from the same vessels, remained in 1.2 mM Mg^{2+}-Krebs throughout the experiment and their bathing fluid was drained and replenished at the same times as in the treated group of strips. Typical kymograph tracings are shown in Figure 1 and the data are summarized in Figure 2. Note the tendency of control strips to gain tone with time, a characteristic of coronary vessels which was described previously (Kalsner, 1975). No statistically significant difference between the tone of the strips in standard and low Mg^{2+}-Krebs was demonstrable until Mg^{2+} was omitted entirely from the Krebs solution (Figure 2). In Krebs containing no added Mg^{2+} (0.0 mM) the mean peak amplitude of the spontaneous tone, determined retrospectively following the routine administration of sodium nitrite (1 mg/ml) at the end of the experiment to achieve full relaxation, was approximately double that obtained in standard Krebs containing 1.2 mM Mg^{2+}. However, when tone was expressed as a percentage of the total contractile capacity of the arteries to a powerful stimulant, such as potassium, it was seen that the increase in Mg^{2+}-free Krebs was really surprisingly small (Figure 2). Thus eight strips responded to 70 mM potassium with a mean contraction amplitude of 86.5 ± 6.7 mm but the spontaneous tone generated in Mg^{2+}- free Krebs was only a mean of 9.6 mm above that of matching control strips maintained in the standard 1.2 mM Mg^{2+}-Krebs (Figure 2).

Other experiments were done in which coronary artery strips, following the initial 120 min equilibration in standard Krebs medium (1.2 mM Mg^{2+}), were incubated for a prolonged period, specifically 3 h, in Krebs containing either 1.2, 0.4, 0.2 or 0.0 mM Mg^{2+}. As shown in Figure 3, all strips gained spontaneous tone over the course of the 3 h test but only those maintained in Krebs with the least Mg^{2+}, namely 0.2 and 0.0 mM Mg^{2+}, showed significantly greater tone than strips maintained in the standard 1.2 mM Mg^{2+}-Krebs during the equivalent 3 h period.

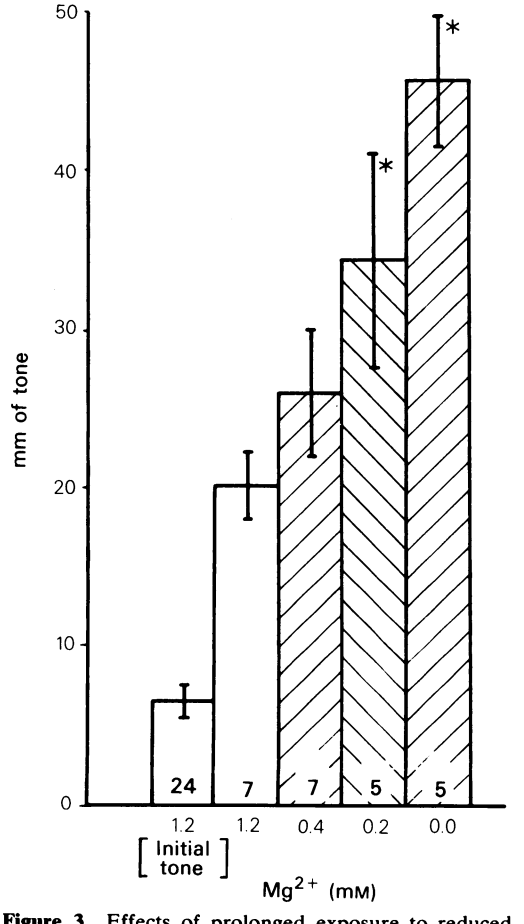

Figure 3 Effects of prolonged exposure to reduced Mg^{2+} on spontaneous tone. After initial equilibration of 24 strips in standard Krebs (1.2 mM Mg^{2+}) for 120 min they were exposed for 3 h to either 1.2, 0.4, 0.2 or 0.0 mM Mg^{2+}-Krebs and the amount of spontaneous tone generated compared. Asterisks indicate values significantly different from strips maintained for 3 h in standard Krebs (1.2 mM Mg^{2+}).

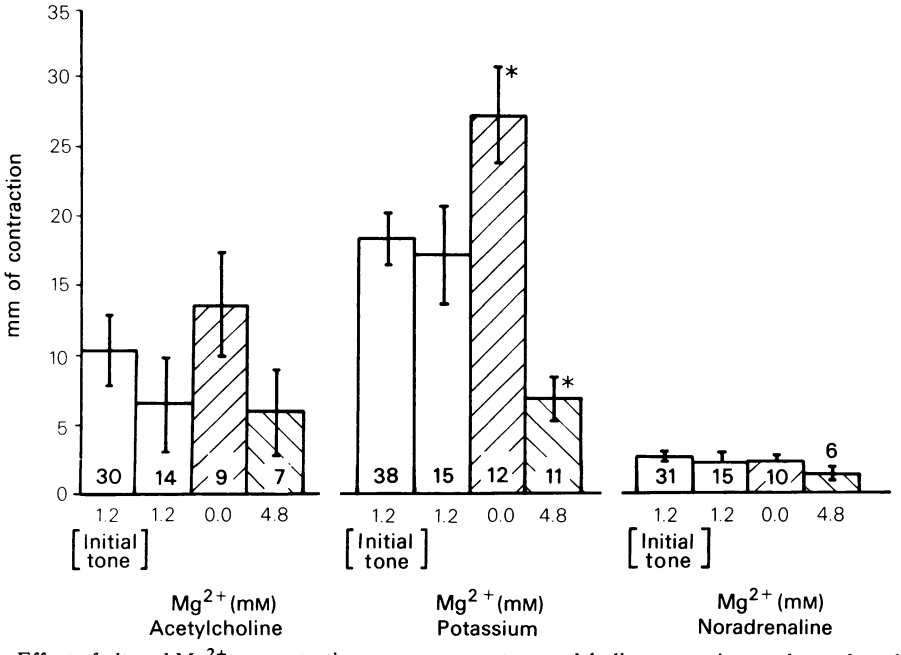

Figure 4 Effect of altered Mg^{2+} concentrations on responses to acetylcholine, potassium and noradrenaline. All strips were initially equilibrated for 120 min in standard Krebs and then the responses to acetylcholine (200 ng/ml), in the presence of physostigmine (0.1 μg/ml), to potassium 15 mM, and to noradrenaline (0.1 μg/ml) in the presence of propranolol (0.5 μg/ml) obtained. This was followed by immersion in Krebs containing the desired Mg^{2+} concentration (0.0, 4.8 or 1.2 mM) and about 40 min later by repetition of the same sequence of agonist administrations. Details are described in text. Asterisks indicate values significantly different from those of the corresponding group kept in standard Krebs.

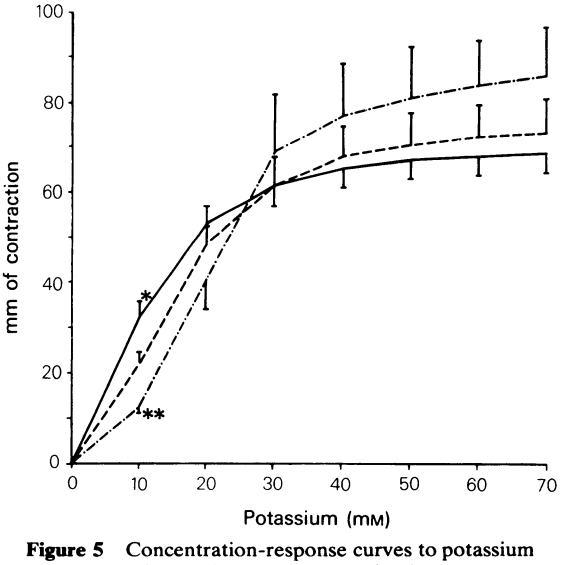

Figure 5 Concentration-response curves to potassium in standard (1.2 mM) (---), 0.0 mM (——) and 4.8 mM (-·-) Mg^{2+}-Krebs solution. Asterisks indicate values significantly different from controls. Number of strips in each group are 11, 8 and 8 respectively.

Responses to agonists

Contractions to three stimulants each acting through different mechanisms to contract the coronary artery muscle were compared in standard, Mg^{2+}-free and high Mg^{2+} (4.8 mM)-Krebs (Figure 4). Responses to acetylcholine (200 mg/ml; in the presence of the cholinesterase inhibitor, physostigmine, to potassium (15 mM) and to noradrenaline (0.1 μg/ml; in the presence of the β-adrenoceptor antagonist propranolol) were first obtained sequentially, with approximately 20 min between contractions in standard Krebs (containing 1.2 mM Mg^{2+}) and then the same sequence was repeated beginning approximately 40 min after immersion in the desired Krebs medium (containing either 0.0, 4.8 or 1.2 mM Mg^{2+}). Responses to acetylcholine and to noradrenaline were not substantially changed in Krebs containing 4.8 or 0.0 mM Mg^{2+} (Figure 4) but those to potassium were enhanced in 0.0 mM Mg^{2+} and depressed in high Mg^{2+}-Krebs.

Concentration-response curves to potassium and 5-hydroxytryptamine

Coronary artery strips were first equilibrated for

Table 1 Effects of 5-hydroxytryptamine (5-HT) and potassium (K^+) on the contractions of bovine coronary arteries in Krebs containing 1.2 mM, 0.0 mM or 4.8 mM Mg

(A) *5-HT*		*No. of strips*	*Geometric mean* (ED_{20mm}*)	*Ratio of* ED_{20s}†	P†	*No. of strips*	*Geometric mean* (ED_{40mm}*)	*Ratio of* ED_{40s}†	P†
Control	(1.2 mM)	13	$9.54 \pm 0.75 \times 10^{-8}$			10	$2.46 \pm 0.75 \times 10^{-7}$		
High Mg^{2+}	(4.8 mM)	18	$1.35 \pm 0.80 \times 10^{-7}$	1.42	<0.4	16	$5.13 \pm 0.79 \times 10^{-7}$	2.09	<0.1
Low Mg^{2+}	(0.0 mM)	18	$4.07 \pm 0.75 \times 10^{-8}$	0.43	<0.1	16	$1.89 \pm 0.65 \times 10^{-7}$	0.77	>0.5
(B) K^+		*No. of strips*	*Geometric mean* (ED_{30mm}*)	*Ratio of* ED_{30s}†	P†	*No. of strips*	*Geometric mean* (ED_{50mm}*)	*Ratio of* ED_{50s}†	P†
Control	(1.2 mM)	11	13.7 ± 1.12			9	23.2 ± 1.18		
High Mg^{2+}	(4.8 mM)	8	17.0 ± 1.08	1.24	<0.2	8	25.4 ± 1.12	1.10	>0.5
Low Mg^{2+}	(0.0 mM)	8	9.8 ± 1.11	0.71	<0.05	8	19.5 ± 1.15	0.84	>0.5

* Means of concentrations of 5HT(g/ml) and of K^+(mM) producing the indicated response size in mm as determined separately for each strip. Results shown with standard errors of the mean. † Comparison made with matching control group.

120 min in standard Krebs solution containing 1.2 mM Mg^{2+} and one group of them was then immersed in Mg^{2+}-free (0.0 mM) Krebs and another in high Mg^{2+} (4.8 mM) Krebs with the third group maintained in the standard Krebs solution. This was followed 20 min later by the sequential addition of increasing concentrations of potassium ranging from 10 mM to 70 mM. As shown in Figure 5, responses to potassium were enhanced in low and decreased in high Mg^{2+}-Krebs but only at the lower portions of the concentration-response curves. An analysis of the concentrations of potassium needed to elicit 30 mm or 50 mm responses, by calculation of geometric means, confirmed that sensitization was limited to the lower part of the concentration-response curve (Table 1).

A protocol similar to the one used to study potassium was employed to assess responses to 5-hydroxytryptamine under conditions of low and high environmental Mg^{2+} (Figure 6). Responses to the agonist were increased significantly over the low to mid dose-range of the curve in Mg^{2+}-free Krebs and depressed in Krebs with high Mg^{2+}. This trend was confirmed by analysis of the geometric means, although statistical significance was not quite reached by this method of analysis (Table 1).

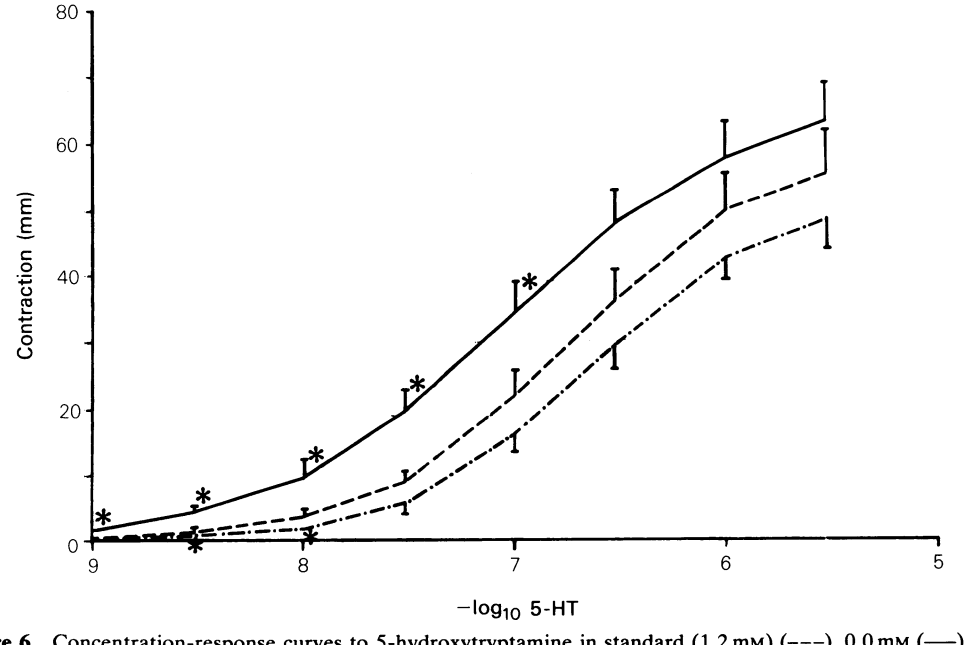

Figure 6 Concentration-response curves to 5-hydroxytryptamine in standard (1.2 mM) (---), 0.0 mM (——) and 4.8 mM (-·-) Mg^{2+}-Krebs solution. Asterisks indicate values significantly different from controls. Number of strips in each group are 14, 18 and 20 respectively.

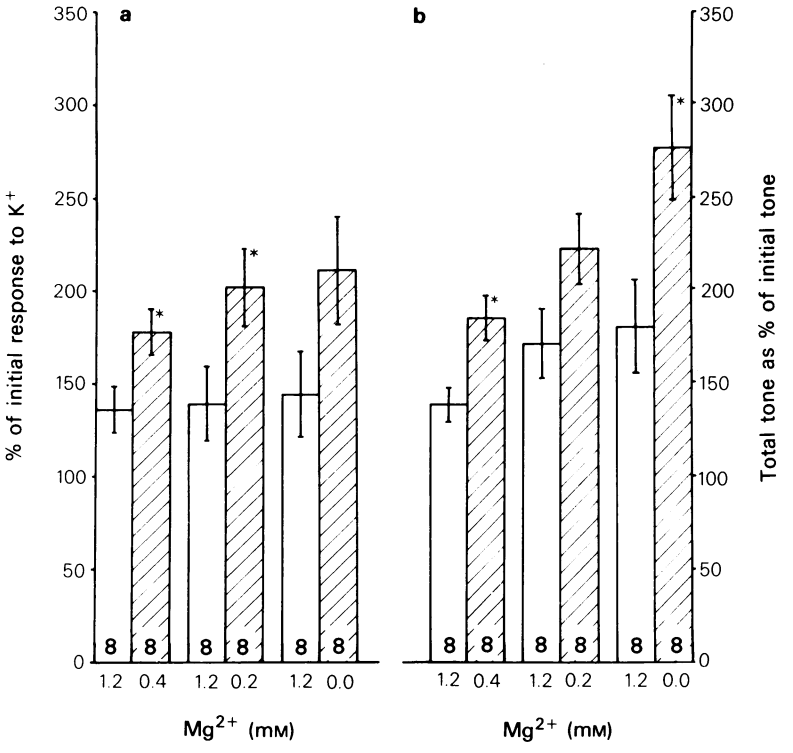

Figure 7 Effects of reduced Mg^{2+} on responses of coronary artery strips to potassium. Strips (hatched columns) were equilibrated for 120 min in standard Krebs (1.2 mM Mg^{2+}) contracted with potassium 10 mM and then immersed sequentially in 0.4, 0.2 and 0.0 mM Mg^{2+} and re-tested with potassium as described in text. A second group (open columns) remained in 1.2 mM Mg^{2+}-Krebs solution throughout the experiment and was contracted with potassium simultaneously with the experimental strips. (a) Data expressed as percentage of initial contraction amplitudes to potassium 120 min after mounting in standard Krebs; (b) same data expressed in terms of total tone of the strips (spontaneous plus potassium-induced). Asterisks indicate contraction values significantly different from those of matched strips maintained in the standard Krebs medium.

Responses to agonists in Krebs with decreased Mg^{2+}

Responses to potassium were assessed under conditions in which the concentration of Mg^{2+} in the Krebs solution was greatly reduced but not entirely omitted. Following the standard 120 min equilibration period, responses to 10 mM potassium were first obtained in 16 strips in standard Mg^{2+}-Krebs. Eight of the strips were then exposed for 30–40 min to 0.4 mM Mg^{2+}-Krebs and the response to 10 mM potassium obtained again followed by washout and exposure to 0.2 mM Mg^{2+}-Krebs for 30 min and then potassium and finally the tissues were immersed in 0.0 mM Mg^{2+}-Krebs for 30 min and the responses to potassium again recorded. The other eight strips remained in 1.2 mM Mg^{2+} throughout the course of the experiment and were tested with potassium 10 mM at the same time as were the experimental strips. The results are shown in Figure 7.

Figure 7a shows the response magnitude to potassium during the course of the experimental protocol, as a percentage of the initial value to potassium recorded for each strip 120 min after mounting in chambers. These initial values averaged 16.3 ± 2.5 mm for the control group and 16.5 ± 1.8 mm for the group subsequently subjected to decreasing Mg^{2+} levels. The magnitude of contraction to potassium were enhanced, but only modestly, in low Mg^{2+}-Krebs. For example, contractions averaged 28.8 ± 2.9 mm when the Mg^{2+} was reduced to 0.4 mM and 20.8 ± 2.0 mm for the matching set of controls. However, the mean potassium contraction amplitude in Mg^{2+}-free Krebs did not differ significantly from controls, probably due to the size of the standard error bars. The data were also expressed in terms of total tone of the coronary artery strips (spontaneous tone plus potassium-induced) under the various test conditions. The initial values in the control group and in the group subsequently exposed to low magnesium were 24.1 ± 3.1 mm and

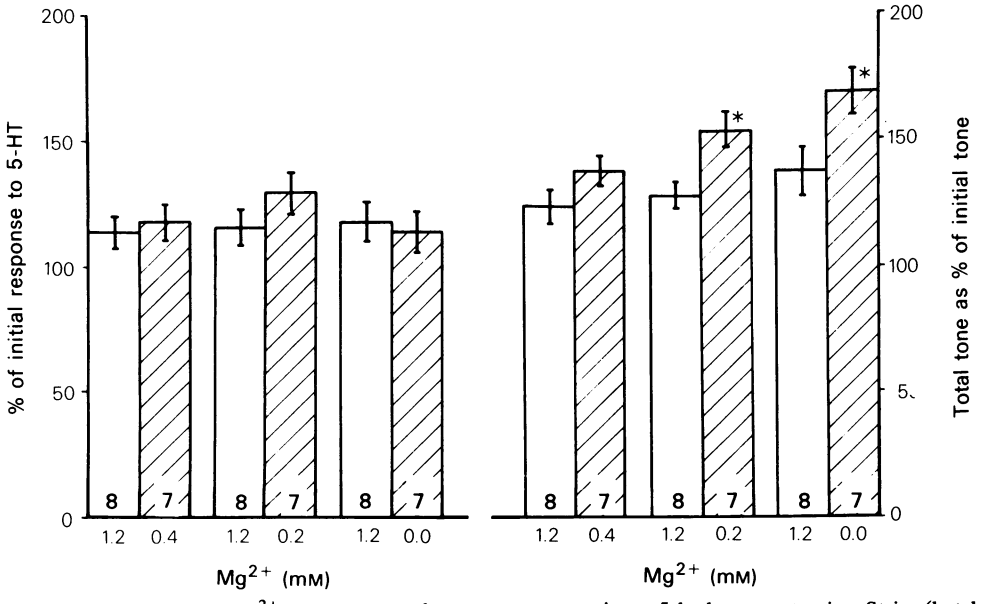

Figure 8 Effects of reduced Mg^{2+} on responses of coronary artery strips to 5-hydroxytryptamine. Strips (hatched columns) were equilibrated for 120 min in standard Krebs (1.2 mM Mg^{2+}) contracted with 5-hydroxytryptamine (5-HT) (0.2 μg/ml) and then immersed sequentially in 0.4, 0.2 and 0.0 mM Mg^{2+}-Krebs and re-tested with 5-hydroxytryptamine as described in text. A second group (open columns) remained in 1.2 mM Mg^{2+}-Krebs throughout the experiment and was contracted with 5-HT simultaneously with the experimental strips. (a) Data expressed as percentage of initial contraction amplitudes to 5-hydroxytryptamine 120 min after mounting in standard Krebs; (b) same data expressed in terms of total tone of the strips (spontaneous plus 5-HT-induced). Asterisks indicate contraction values significantly different from those of matched strips maintained in the standard Krebs medium.

24.3 ± 2.7 mm respectively. Differences in total tone between control and treated groups were not substantial until the Mg^{2+} was omitted from the Krebs, although a slight effect was evident at 0.4 mM Mg^{2+}.

A similar protocol was used to study the effect of diminished Mg^{2+} on more sizeable contractions elicited by a moderate concentration of 5-hydroxytryptamine (0.2 μg/ml). As can be seen in Figure 8, responses to 5-hydroxytryptamine, with initial means of 52.3 ± 6.0 mm in the control and 40.9 ± 3.9 mm in the experimental group, were not altered significantly during the course of exposure to reduced Mg^{2+}. When the total tone (spontaneous plus 5-hydroxytryptamine-induced) was examined, a modest increment over controls was noted in the groups exposed to 0.2 mM or 0.0 mM Mg^{2+}-Krebs, but this is probably a direct effect of the diminished Mg^{2+} on spontaneous or basal tone, as was already described above.

Discussion

The present results indicate that reductions in extracellular magnesium must be extreme in order to increase substantially the tone of coronary artery strips. Even a complete absence of the cation in the Krebs for 30 min led to only modest increases in spontaneous tone and following 3 h of immersion in magnesium-deficient Krebs, down to as low as 0.4 mM, the tone of the vessels was not increased above controls. Significant tone increments, attributable to magnesium deficiency, required prolonged periods of immersion in magnesium-deficient Krebs and major reductions in the concentration of the mineral, down to 0.2 mM.

Contractions of coronary artery strips induced by the sympathetic nerve transmitter, noradrenaline, were not magnified in Krebs with diminished magnesium; not even when the magnesium was entirely omitted from the formula. Contractions to acetylcholine also were not significantly enlarged in magnesium-free Krebs. Responses to potassium and to 5-hydroxytryptamine were increased in magnesium-free Krebs but only with respect to the lower portions of their concentration-response curves. Fujiwara, Kitagawa & Kurahashi (1978) also noted that small responses to potassium were enhanced but large contractions depressed when rabbit aorta was immersed in magnesium-free Krebs.

Previously, Jurevics & Carrier (1973) reported

that responses of rabbit aorta to acetylcholine were increased in magnesium-free Krebs but that those to noradrenaline were not. Similarly, Altura & Altura (1971), even earlier, had noted that in magnesium-free Krebs, responses of rabbit aorta to adrenaline were depressed and those to acetylcholine increased, whereas responses to some other test agonists did not seem to be changed. Most recently Turlapaty & Altura (1980) confirmed the applicability of their observations about enhanced contractions in magnesium-free Krebs to dog coronary artery strips and proposed that, what they term, 'ischaemic heart disease sudden death' might be attributable to the contraction or spasm of coronary arteries induced by an environment of reduced magnesium. However, their experimental evidence was obtained in the extreme condition in which magnesium was totally omitted from the Krebs and, further, the amount of the tone changes induced in a number of instances, as presented in their paper, seem meagre when placed in the overall perspective of coronary artery contractile performance. Neither the amount of the tone changes nor the extremity of magnesium deprivation used to demonstrate such changes seems adequate to explain coronary artery spasm and sudden death in humans. Experiments described here, in which the magnesium content of the Krebs was progressively reduced, confirmed that almost total abolition of magnesium was required for substantial magnification of contraction magnitudes, even to susceptible agonists.

In order to interpret the present data in the context of human magnesium deficiency it is necessary to comment briefly on what has been called 'the water story'; namely the hypothesis that a deficiency of some mineral in soft water or the presence of some factor in hard water accounts for an increased incidence of heart disease in certain localities (e.g. Anderson *et al.*, 1975; Chipperfield & Chipperfield, 1977). When the present findings, together with other available information are taken into consideration it seems improbable that variations in the magnesium content of drinking water could conceivably be sufficient to explain regional differences in cardiovascular mortality. Firstly, the major dietary source of magnesium is food, including a variety of processed and snack foods, and only a small amount, at most 12%, comes from water (Hankin, Margen & Goldsmith, 1970). These workers also noted during their detailed study of the magnesium content of foods, that residence in a hard water area did not ensure an intake of only hard water since 'approximately half of our subjects drank softened or treated water at home'. Further, the normal plasma magnesium level, generally regarded to fall within the range of 1.63–1.78 mEq/l, has been established by a number of studies to be remarkably constant within and between normal individuals (Nordin, 1976a; Aikawa, 1978). Nordin (1976b) comments convincingly that 'any diet providing enough nutrients to support life would also contain enough magnesium' since conservation mechanisms in the body would ensure that normal body levels are maintained. Distinctly abnormal plasma values (i.e. 0.5–0.7 mEq/l) are rarely encountered, except in conditions such as renal failure, acute alcoholism and malabsorption states (Shils, 1969; Nordin, 1976b; Aikawa, 1978) and they are accompanied by muscle tremor, ataxia, mental confusion, delirium and even seizures (Loeb, Pietras, Gunnar & Tobin, 1968; Aikawa, 1978). Clearly, several groups of workers already regard the association of cardiovascular death with magnesium deficiency as unproven and possibly 'spurious' or coincidental (Punsar, 1973; Comstock, 1978).

It seems clear, from the present findings and the literature surveyed above, that there is a general misunderstanding about the amount of decrease in plasma and tissue magnesium reported in hypertension and certain cardiac states and the degree of deficiency necessary for changes in coronary dynamics. For example, one report (Beller, Maher, Hartley, Bass & Wacker, 1972) showed that plasma magnesium dropped from 24.2 to 23.3 mg/l during vigorous exercise for 90 min but such a trivial change in magnesium could not be expected to influence coronary tone, if the present findings are to serve as a guide. In the same way, Bauer, Martin & Mickey (1965) reported that hypertensive men (but not women) had serum values of 1.5 mEq/l compared to 1.7 mEq/l in normotensive individuals. Albert, Morita & Iseri (1958) found plasma magnesium values to average 1.4 mEq/l in hypertensives and 1.6 mEq/l in normotensives and they noted that the magnitude of the depression in magnesium did not correlate with the severity of the hypertension. Such modest differences may be attributed to renal or hormonal complications of the hypertension rather than to any dietary deficiency (Haury & Cantarow, 1942). Similarly, patients with severe and moderate coronary artery disease were reported by Manthey, Stoeppler, Morgenstern, Nussel, Opherk, Weintraut, Wesch & Kubler (1981) to have serum plasma magnesium levels averaging 1.63 mEq/l and 1.72 mEq/l respectively compared to 1.78 mEq/l in controls. These are differences obviously insufficient to account for substantial variations in coronary tone and even such meagre deficits are arguable and not at all well established (e.g. Abraham, Weinstein, Eylath & Czackes, 1978; Dyckner, 1980) and possibly a consequence of the infarction rather than its cause (Nath, Sikka, Sur, Saxena & Srivastava, 1969; Seelig & Heggtveit, 1974).

Other workers have measured the magnesium content of cardiac tissue in attempts to relate the cellular

content of the cation to the incidence of infarction (see Seelig & Heggtveit, 1974). For example, Anderson *et al.* (1975) found that the mean myocardial magnesium content of those who died from ischaemic heart disease was 22% lower than those dead from accidental causes, a finding similar to that reported earlier (Heggtveit, Tanser & Hunt, 1969), where the difference between the two groups was 19%. In yet another study, victims of a fatal first coronary event had a mean myocardial magnesium value of 191 μg/g compared to 216 μg/g in those dead from accidental causes and 212 μg/g in those dead from long-standing ischaemic heart disease (Behr & Burton, 1973) and essentially similar findings were reported by others (Chipperfield & Chipperfield, 1973; Johnson, Peterson & Smith, 1979). However, the relevance of these data to the participation of magnesium in infarction is far from clear and not solely because of the small amount of the magnesium depletion. It is well known that even a few minutes of anoxia may lead to a loss of intracellular cations in cardiac tissue (e.g. magnesium and potassium) (Singh, Flear, Nandra & Ross, 1972; Chipperfield & Chipperfield, 1977) and, consequently, magnesium depletion of myocardium may well be a consequence of the hypoxic event initiated by spasm of presently undetermined origin (Karppanen *et al.*, 1978) rather than its cause. According to Polimeni (1975) 'electrolyte redistributions do not cause cardiac arrest but are a consequence of agonal ischaemia'. The loss of myocardial magnesium associated with oxygen deficiency may represent deletion of groups of myocardial cells (Polimeni & Page, 1973) rather than a uniform loss from the myocardial mass in general.

It appears from the present study and the available reports on tissue and plasma magnesium values in cardiac victims that any deficiency of the mineral that may exist is insufficient to induce coronary artery constriction of a magnitude, either directly or through sensitization of the response to circulating or nerve-released vasoactive substances, such that it could explain sudden death or myocardial infarction.

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