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INHIBITION BY Cd^{2+}, VERAPAMIL AND PAPAVERINE OF Ca^{2+}-INDUCED CONTRACTIONS IN ISOLATED CEREBRAL AND PERIPHERAL ARTERIES OF THE DOG

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1 In helically cut strips of canine cerebral arteries exposed to Ca^{2+}-free media and depolarized by K^+, the addition of Ca^{2+} caused biphasic (transient and sustained) contractions, while in coronary and mesenteric arteries, the addition of Ca^{2+} produced a sustained contraction sometimes preceded by a slight transient contraction.

2 These Ca^{2+}-induced contractions were attenuated by Cd^{2+} (5 to 100 μM) in a dose-dependent manner, the attenuation being greater in cerebral than in coronary and mesenteric arteries. The inhibitory effect of Cd^{2+} was prevented and partially reversed by 1 mM cysteine.

3 Verapamil and papaverine were also effective in attenuating the Ca^{2+}-induced contractions in cerebral and peripheral arteries: susceptibility to verapamil was in the order, cerebral > coronary > mesenteric, while that to papaverine was in the order, cerebral = coronary > mesenteric.

4 It may be concluded that the agents that interfere with trans-membrane influxes of Ca^{2+} cause a greater relaxation in cerebral than in peripheral arteries, as is seen with papaverine, a non-specific vasodilator.

Introduction

It has already been shown that cerebral arterial smooth muscles both from man and animals respond differently from peripheral arterial smooth muscles when vasoconstrictor and vasodilator agents are applied (Bohr, Goulet & Taquini, 1961; Uchida, Bohr & Hoobler, 1967; Toda & Fujita, 1973; Toda, 1974a; Dalske, Harakal, Sery & Menkowitz, 1974; Müller-Schweinitzer, 1976). Our previous data showed that a triphasic pattern of responses, a rapid contraction, rapid relaxation, and sustained contraction, is induced by the addition of Ca^{2+} in isolated cerebral arteries of the dog after a long exposure to Ca^{2+}-free media including excess K^+ (Toda, 1974b). This pattern of responses clearly differs from that observed in peripheral arteries.

Cadmium ions and verapamil interfere with the influx of Ca^{2+} across cell membranes in cardiac and vascular smooth muscles (Fleckenstein, Tritthard, Fleckenstein, Herbst & Gruen, 1969; Kaufmann, Tritthart, Rost & Fleckenstein, 1970; Toda, 1973a; 1976a), resulting in vasodilatation. On the other hand, papaverine causes a relaxation of smooth muscles by mechanisms relating not only to influxes of Ca^{2+} but also to intracellular Ca^{2+} sequestration (Carpenedo, Toson, Furlanut & Ferrari, 1970; Tashiro & Tomita, 1970) and oxidative phosphorylation (Santi, Ferrari & Contessa, 1964; Ferrari & Carpenedo, 1968).

The present study was undertaken to determine the inhibitory effect of Cd^{2+}, verapamil and papaverine on arterial contractions induced by Ca^{2+} and to evaluate the susceptibility of canine cerebral and peripheral arteries to vasodilator agents acting directly on vascular smooth muscle cells.

Methods

Mongrel dogs of either sex, weighing between 7 to 16 kg, were anaesthetized with intraperitoneal injections of sodium pentobarbitone in a dose of 50 mg/kg and were killed by bleeding from the common carotid arteries. The brain and heart were rapidly removed, and the basilar and middle cerebral arteries (0.6 to 0.9 mm outside diameter) and the ventral interventricular branch of left coronary arteries (0.6 to 0.9 mm) were isolated. The distal portion of the superior mesenteric arteries (0.6 to 1.0 mm) was also isolated. The basilar and middle cerebral arteries responded to vasoactive agents in the same way; therefore, the term 'cerebral arteries' in this

paper includes both arteries. The specimen was cut helically into strips approximately 20 mm long. These strips were fixed vertically between hooks under a resting tension of 1.5 g in a muscle bath of 20 ml capacity, containing the nutrient solution. Hooks anchoring the upper end of the strip were connected to the lever of a force-displacement transducer (Nihonkoden Kogyo Co., Tokyo, Japan). The bathing fluid was aerated with a mixture of 95% O_2 and 5% CO_2 and maintained at 37 ± 0.5°C. The composition of the solution was as follows (mM): Na^+ 162.1, K^+ 5.4, Ca^{2+} 2.2, Cl^- 157.0, HCO_3^- 14.9, and glucose 5.6. The pH of the solutions was 7.2 to 7.3. In order to raise external concentrations of K^+, the KCl solution was added directly to the bathing media. Osmotic adjustment was not made when external K^+ was raised and external Ca^{2+} was removed. The preparations were allowed to equilibrate for 90 to 120 min in control media and during the equilibration period, the bathing media were replaced every 15 to 20 minutes.

Isometric contractions of arterial strips were displayed on an ink-writing oscillograph (Sanei Sokki Co., Tokyo, Japan). The contractile response to 25 mM K^+ was first obtained and the preparations were washed three times with normal fluid. After an equilibration period of 35 to 45 min, preparations were exposed for 60 min to Ca^{2+}-free media, during which time the solution was replaced twice every 20 min, and K^+ (25 mM) was added. After the K^+-induced contraction levelled off, Ca^{2+} in a concentration of 2.2 mM was added. Some preparations were treated for 20 min with blocking agents, before the addition of K^+. Contractions induced by Ca^{2+} relative to those by K^+ (25 mM) in control media in the same preparations were calculated. The values obtained in the presence and absence of treatment with blocking agents were compared. Results shown in the text, tables and figures represent mean values ± s.e. means. Statistical analyses in paired preparations were made using Student's *t* test.

Drugs used were verapamil hydrochloride (Eisai Pharmaceutical Co., Tokyo, Japan), papaverine hydrochloride, L-cysteine hydrochloride and glutathione.

Results

Comparisons of the response to Ca^{2+} in cerebral, coronary and mesenteric arteries

In helically cut strips of cerebral arteries exposed for 60 min to Ca^{2+}-free media and depolarized by 25 mM K^+, the addition of 2.2 mM Ca^{2+} caused a phasic contraction followed by sustained contraction (Figure 1). Such a phasic contraction was also elicited by Ca^{2+} in Ca^{2+}-free media in the absence of the

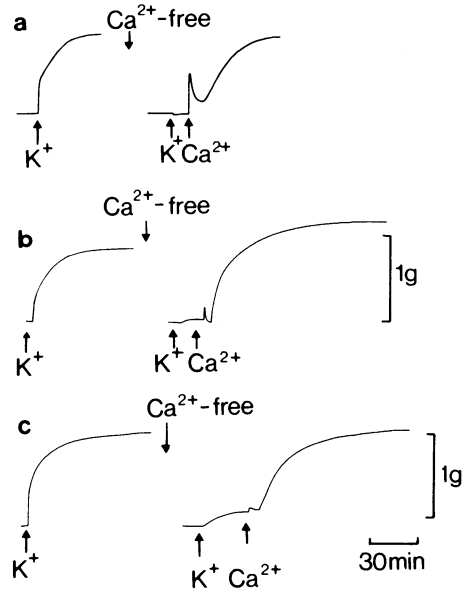

Figure 1 Comparison of the effect of K^+ and Ca^{2+} on (a) basilar (b) coronary and (c) mesenteric arteries isolated from the same dog. The response to K^+ (25 mM) was first obtained in control media. Preparations were then exposed for 60 min to Ca^{2+}-free media, and K^+ (25 mM) and Ca^{2+} (2.2 mM) were added successively.

treatment with 25 mM K^+ (Table 1). In coronary and mesenteric arterial strips exposed to Ca^{2+}-free media and treated with 25 mM K^+, the addition of Ca^{2+} caused a sustained contraction which was sometimes preceded by a slight, phasic contraction (Figure 1).

Contractile responses of these arteries to K^+ and Ca^{2+} in Ca^{2+} (2.2 mM)-containing and Ca^{2+}-free media are summarized in Figure 2. Contractions induced by K^+ in Ca^{2+}-free media were appreciably less in cerebral than in coronary and mesenteric arteries, and phasic contractions by Ca^{2+}, shown as 'A' on the abscissa scale in Figure 2, were significantly greater.

Inhibition by Cd^{2+} of the Ca^{2+}-induced contraction

Treatment with Cd^{2+} (5 to 100 μM) caused a slight, persistent relaxation. This relaxation was not dependent upon concentrations of Cd^{2+}, because the preparations relaxed almost completely in control media, therefore relaxation induced by vasodilator agents was always slight and inconsistent from preparation to preparation.

The contractile response of cerebral arteries to Ca^{2+} was reduced by treatment for 20 min with Cd^{2+} (5 to 100 μM) in a dose-dependent manner (Table 1). Both the phasic and sustained contractions were attenuated,

Table 1 Inhibition by Cd^{++} of the Ca^{++}-induced contraction in isolated cerebral, coronary and mesenteric arteries

Arteries and conditions	n	K^+ 25 mM	Ca^{2+} removal	Cd^{2+}	K^+ 25 mM	*Responses (mg) to* Ca^{2+} 2.2 mM *A*	*B*	*C*	*Cysteine 1 mM*	*Cysteine + Ca^{2+}*
Cerebral										
Control	23	838 ± 70	−110 ± 27		24 ± 9	436 ± 66 (53 ± 4.7%)	160 ± 26	880 ± 69 (110 ± 5.1%)	−378 ± 101	505 ± 62 (61 ± 4.9%)
Control*	8	806 ± 118	−68 ± 30			416 ± 16 (51 ± 5.3%)	246 ± 96			
Cd^{2+} 5 μM	13	896 ± 128	−180 ± 54	−48 ± 17	26 ± 9	350 ± 59 (39 ± 6.9%)	18 ± 3	576 ± 95 (67 ± 6.9%)**	466 ± 91 (52 ± 12%)	920 ± 116 (108 ± 5.1%)
Cd^{2+} 20 μM	17	720 ± 67	−144 ± 43	−36 ± 12	60 ± 19	68 ± 29 (7.6 ± 3.2%)**	19 ± 9	132 ± 38 (19 ± 5.1%)**	272 ± 76 (39 ± 9.0%)	420 ± 76 (59 ± 8.3%)
Cd^{2+} 100 μM	6	787 ± 147	−146 ± 65	−74 ± 19	0	0 (0%)**	0	0 (0%)**	103 ± 58 (14 ± 5.9%)	103 ± 58 (14 ± 5.9%)
Coronary										
Control	26	930 ± 72	−32 ± 26		48 ± 14			1136 ± 78 (117 ± 4.9%)	−330 ± 62	809 ± 93 (88 ± 5.3%)
Cd^{2+} 5 μM	9	910 ± 70	−58 ± 18	−6 ± 3	3 ± 2			1010 ± 102 (110 ± 6.6%)	−318 ± 49	705 ± 68 (78 ± 7.6%)
Cd^{2+} 20 μM	10	1236 ± 115	−202 ± 82	−118 ± 44	0			504 ± 112 (40 ± 7.2%)**	306 ± 57 (27 ± 5.7%)	810 ± 102 (67 ± 6.2%)
Cd^{2+} 100 μM	5	1502 ± 297	−342 ± 143	−50 ± 15	4 ± 2			2 ± 2 (0%)**	660 ± 165 (49 ± 10%)	661 ± 165 (49 ± 10%)
Mesenteric										
Control	27	953 ± 99	−42 ± 22		163 ± 28			918 ± 95 (98 ± 5.4%)	−195 ± 81	725 ± 93 (77 ± 6.2%)
Cd^{2+} 5 μM	9	1192 ± 176	−56 ± 23	−9 ± 3	78 ± 66			1053 ± 195 (87 ± 7.2%)	210 ± 90 (20 ± 10%)	1241 ± 141 (113 ± 11%)
Cd^{2+} 20 μM	8	1860 ± 212	−120 ± 50	−76 ± 52	52 ± 16			1097 ± 233 (59 ± 11%)*	544 ± 122 (28 ± 5.9%)	1641 ± 220 (87 ± 8.0%)
Cd^{2+} 100 μM	7	1668 ± 202	−50 ± 41	−66 ± 18	90 ± 23			37 ± 22 (2.0 ± 1.3%)**	1002 ± 113 (67 ± 10%)	1058 ± 127 (68 ± 10%)

Control* in cerebral arteries; Contractions induced by Ca^{2+} were obtained in Ca^{2+}-free media without the addition of K^+ (values obtained in the previous study, Toda, 1974b). A, B, C: see the legend for Figure 2. Numbers in parentheses indicate the contractions relative to those induced by 25 mM K^+ in control media. Minus indicates relaxation.
Significantly different from respective controls, $^{**}P < 0.001$; $^{*}P < 0.01$.

Table 2 Inhibition by verapamil of the Ca^{2+}-induced contraction in isolated cerebral, coronary and mesenteric arteries of the dog

Arteries and conditions	n	*K^+ 25 mM*	*Ca^{2+}-removal*	*Verapamil*	*K^+ 25 mM*	*Response (mg) to Ca^{2+} 2.2 mM* A	B	C	*+ Ca^{2+} 4.4 mM*	*Ca^{2+} (total)*
Cerebral										
Control	23	838 ± 70	−110 ± 27		24 ± 9	436 ± 66 (53 ± 4.7%)	160 ± 26	880 ± 69 (110 ± 5:1%)	−104 ± 20	771 ± 61 (92 ± 5.2%)
Verapamil 50 nM	10	1348 ± 117	−184 ± 90	−86 ± 21	12 ± 7	282 ± 82 (20 ± 5.5%)**	226 ± 88	650 ± 83 (49 ± 4.1%)**	8 ± 32	658 ± 78 (50 ± 5.0%)
Verapamil 0.2 μM	7	1054 ± 228	−140 ± 43	−52 ± 16	10 ± 14	90 ± 68 (8.6 ± 2.1%)**	70 ± 52	212 ± 51 (23 ± 4.8%)**	128 ± 29	340 ± 73 (37 ± 5.9%)
Verapamil 1 μM	4	1176 ± 47	−46 ± 22	−40 ± 21	5 ± 2	0	0	46 ± 13 (3.5 ± 0.7%)**	116 ± 65	160 ± 70 (14 ± 5.9%)
Coronary										
Control	26	930 ± 72	−32 ± 26		48 ± 14			1136 ± 78 (117 ± 4.9%)	−120 ± 70	1019 ± 72 (108 ± 4.5%)
Verapamil 50 nM	7	1394 ± 190	−46 ± 15	−24 ± 4	0 ± 56			1104 ± 159 (82 ± 10%)*	58 ± 72	1162 ± 170 (85 ± 7.8%)
Verapamil 0.2 μM	8	1216 ± 243	−40 ± 31	−18 ± 8	4 ± 6			406 ± 109 (32 ± 5.5%)**	250 ± 35	658 ± 119 (59 ± 5.9%)
Verapamil 1 μM	5	980 ± 218	−30 ± 10	−5 ± 3	6 ± 4			32 ± 18 (2.4 ± 1.3%)**	88 ± 28	120 ± 44 (14 ± 3.5%)
Mesenteric										
Control	27	953 ± 99	−42 ± 22		163 ± 28			918 ± 95 (98 ± 5.4%)	−296 ± 109	625 ± 95 (66 ± 4.7%)
Verapamil 50 nM	7	1014 ± 187	−38 ± 3	−10 ± 4	34 ± 16			834 ± 208 (80 ± 7.8%)	−116 ± 46	720 ± 241 (68 ± 10%)
Verapamil 0.2 μM	8	1432 ± 274	−18 ± 7	−14 ± 4	36 ± 13			686 ± 199 (42 ± 6.2%)**	86 ± 73	773 ± 206 (49 ± 4.8%)
Verapamil 1 μM	5	942 ± 106	−33 ± 29	−7 ± 3	16 ± 8			127 ± 65 (14 ± 8.1%)**	144 ± 47	271 ± 108 (31 ± 14%)

A, B, C: see the legend for Figure 2. Numbers in parentheses indicate the contractions relative to those induced by 25 mM K^+ in control media. Minus indicates relaxation.
Significantly different from respective controls, $^{**}P < 0.001$; $^{*}P < 0.01$.

Table 3 Inhibition by papaverine of the Ca^{2+}-induced contraction in isolated cerebral, coronary and mesenteric arteries of the dog.

Arteries and conditions	n	*Response (mg) to* K^+ *25 mM*	Ca^{2+}*-removal*	*Papaverine*	K^+ *25 mM*	Ca^{2+} *2.2 mM* *A*	*B*	*C*
Cerebral								
Control	23	838 ± 70	−110 ± 27		24 ± 9	436 ± 66 (53 ± 4.7%)	160 ± 26	880 ± 69 (110 ± 5.1%)
Papaverine 1 μM	8	608 ± 88	−60 ± 24	−24 ± 4	66 ± 36	300 ± 128 (42 ± 11%)	118 ± 84	528 ± 86 (86 ± 4.3%)†
Papaverine 5 μM	11	822 ± 122	−126 ± 41	−76 ± 23	29 ± 14	162 ± 62 (16 ± 4.4%)**	57 ± 8	360 ± 54 (44 ± 2.1%)**
Papaverine 20 μM	5	1122 ± 216	−144 ± 47	−82 ± 36	12 ± 6	150 ± 46 (12 ± 2.4%)**	14 ± 4	358 ± 62 (31 ± 4.7%)**
Coronary								
Control	26	930 ± 72	−32 ± 26		48 ± 14			1136 ± 78 (117 ± 4.9%)
Papaverine 1 μM	7	1090 ± 114	−60 ± 24	−68 ± 14	86 ± 36			982 ± 182 (88 ± 9.1%)†
Papaverine 5 μM	23	1104 ± 72	−132 ± 45	−148 ± 37	46 ± 13			622 ± 110 (56 ± 4.9%)**
Papaverine 20 μM	11	1304 ± 198	−102 ± 38	−148 ± 24	5 ± 2			502 ± 129 (38 ± 4.9%)**
Mesenteric								
Control	27	953 ± 99	−40 ± 22		163 ± 28			918 ± 95 (98 ± 5.4%)
Papaverine 1 μM	4	1138 ± 284	−65 ± 28	−15 ± 9	163 ± 77			1156 ± 332 (98 ± 3.6%)
Papaverine 5 μM	15	1374 ± 126	−44 ± 19	−38 ± 9	150 ± 40			958 ± 113 (71 ± 6.8%)*
Papaverine 20 μM	12	1390 ± 113	−50 ± 20	−82 ± 26	76 ± 34			562 ± 93 (40 ± 6.0%)**

A, B, C: see the legend for Figure 2. Numbers in parentheses indicate the contractions relative to those induced by 25 mM K^+ in control media. Minus indicates relaxation.
Significantly different from respective controls, $^{**}P < 0.001$; $^{*}P < 0.01$; $^{\dagger}P < 0.02$.

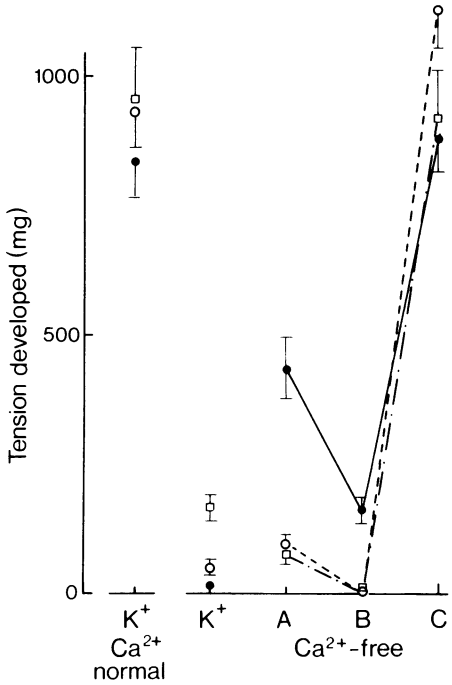

Figure 2 Contractile responses to K^+ and Ca^{2+} of cerebral (●), coronary (○) and mesenteric (□) arteries exposed to control and Ca^{2+}-free media. Concentration of K^+:25 mM. A, initial contraction induced by 2.2 mM Ca^{2+}; B, level of the minimum tension developed following the addition of Ca^{2+}; C, sustained contraction induced by Ca^{2+}. Vertical bars represent standard errors of the means. Number of preparations used: cerebral 23; coronary 26; mesenteric arteries 27.

although the inhibition of the former contraction by Cd^{2+} 5 μM was insignificant. After the Ca^{2+}-induced sustained contraction levelled off, cysteine (1 mM) or glutathione (1 mM) produced a relaxation in control preparations but a contraction in Cd^{2+}-treated arteries. In 8 out of 17 preparations treated with 20 μM Cd^{2+}, cysteine caused a biphasic pattern of contractions. Calcium ions (4.4 mM) failed to reverse the Cd^{2+}-induced inhibition. Typical recordings for the inhibitory effect of Cd^{2+} and the reversal by cysteine are demonstrated in Figure 3. Prior treatment with cysteine (1 mM) completely prevented the inhibitory effect of 20 μM Cd^{2+}.

Treatment with Cd^{2+} in concentrations higher than 20 μM caused a significant inhibition in the contractile response to Ca^{2+} of coronary and mesenteric arteries (Table 1). Inhibition by 5 and 20 μM Cd^{2+} was considerably less in coronary and mesenteric arteries than in cerebral arteries (Figure 4, left). Mean ID_{50}s in cerebral, coronary and mesenteric arteries were 6.2, 13.8 and 23.6 μM, respectively. The inhibitory effect of Cd^{2+} was partially reversed by 1 mM cysteine.

Inhibition by verapamil of the Ca^{2+}-induced contraction

Treatment for 20 min with verapamil in concentrations ranging from 50 nM to 1 μM caused a dose-related inhibition in both the phasic and sustained contractions induced by Ca^{2+} in cerebral arterial strips exposed to Ca^{2+}-free media (Table 2). After Ca^{2+}-induced contractions levelled off, the addition of a further 4.4 mM Ca^{2+} elicited a relaxation in control arteries but a contraction in verapamil-treated strips. Cysteine was ineffective in reversing the inhibitory effect of verapamil.

Verapamil in a concentration of 50 nM attenuated the contractile response of coronary arteries to Ca^{2+} to an appreciably lesser extent than that of cerebral arteries, and this concentration of verapamil failed to attenuate significantly the response in mesenteric arteries (Table 2). Comparisons of the inhibitory effect of verapamil in these arteries is shown in Figure 4. Average ID_{50}s in coronary and mesenteric arteries were 0.1 μM and 0.14 μM, while the value in cerebral arteries was less than 50 nM.

Inhibition by papaverine of the Ca^{2+}-induced contraction

Papaverine in concentrations of 1 to 20 μM caused a dose-dependent inhibition in the contractile response of cerebral and coronary arteries to 2.2 mM Ca^{2+}, while in mesenteric arteries, papaverine at 1 μM was ineffective and in concentrations higher than 5 μM significantly attenuated the Ca^{2+}-induced contraction (Table 3). Different susceptibility of the three arteries to papaverine is illustrated in Figure 4. ID_{50}s of cerebral, coronary and mesenteric arteries averaged 3.5, 4.9 and 12 μM, respectively.

Discussion

The addition of Ca^{2+} to isolated cerebral arteries of the dog exposed to Ca^{2+}-free media caused biphasic contractions. The transient contraction (independent of K^+-induced depolarization) is possibly induced by influxes of Ca^{2+} across cell membranes, in which the ion permeability increases following long exposure to Ca^{2+}-free media (Somlyo & Somlyo, 1968), while the sustained contraction may derive from slowly developing increase in Ca^{2+} influxes in association with the membrane depolarization induced by elevated $[K^+]_o$. In the present study, the initial phasic contraction induced by Ca^{2+} was markedly less and the contraction induced by K^+ in Ca^{2+}-free media was greater in coronary and mesenteric arteries than in cerebral arteries. Membrane Ca^{2+} plays a role in

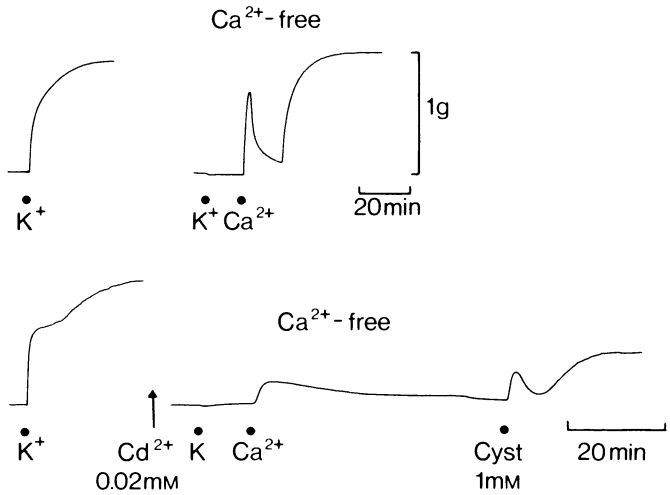

Figure 3 Inhibitory effect of Cd^{2+} on the Ca^{2+}-induced contraction in a basilar artery. Two basilar arterial strips were obtained from the same dog, one for control series of experiments (upper tracings) and the other for experiments with 20 μM Cd^{2+} (lower tracings). In these two strips, contractile responses to 25 mM K^+ were first obtained. Preparations were then exposed for 60 min to Ca^{2+}-free media before the addition of K^+; in the lower tracings, Cd^{2+} was added to the preparation after exposure for 40 min to Ca^{2+}-free media. Cysteine (Cyst) produced a biphasic contraction after Cd^{2+} treatment.

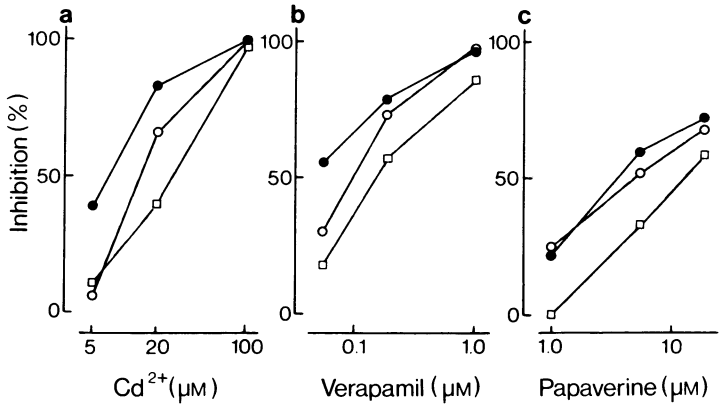

Figure 4 Inhibition by (a) Cd^{2+}, (b) verapamil and (c) papaverine of the Ca^{2+}-induced contraction in cerebral (●), coronary (○) and mesenteric (□) arteries exposed to Ca^{2+}-free media. Each value was obtained from Tables 1, 2 and 3 by comparison of maximum contractions induced by Ca^{2+} relative to those induced by K^+ in preparations exposed to control and experimental media (for instance, in cerebral arteries at 5 μM Cd^{2+}, 67% was expressed as a percentage of 110% and then subtracted from 100%).

stabilizing the membrane (Shanes, 1958) and is also released to cause a vascular contraction by the addition of K^+ (Somlyo & Somlyo, 1968). It appears that membrane Ca^{2+} in cerebral arterial smooth muscle cells is easily depleted by 60 min exposure to Ca^{2+}-free media, as compared with that in coronary and mesenteric arteries, because the response to K^+ was greater in the latter.

Treatment with Cd^{2+}, like verapamil, a known Ca^{2+} antagonist (Fleckenstein *et al.*, 1969) or papaverine, suppressed both the phasic and sustained contractions induced by Ca^{2+} in cerebral arteries, indicating that the Cd^{2+}-induced inhibition does not derive from the antagonism to K^+-induced depolarization. Such non-selective inhibition by Cd^{2+} of the contraction mediated via increased transmembrane influxes of

Ca^{2+} is probably not due to interference with functioning of contractile proteins, since the contractile response of rabbit aortae to noradrenaline, histamine and angiotensin II is inhibited only slightly by Cd^{2+} in concentrations sufficient to cause a marked attenuation of contractions induced by K^+ and Ba^{2+} (Toda, 1973a). Further, contractility of the glycerinated aorta is unaffected by 100 μM Cd^{2+} (unpublished data). Cysteine partially reversed and completely prevented the Cd^{2+}-induced inhibition seen in isolated aortae, atria and sinoatrial nodes of the rabbit (Toda, 1973a,b,c). It may therefore be concluded that Cd^{2+} interferes with transmembrane influxes of Ca^{2+} by a mechanism related to membrane SH groups. In fact, influxes of $^{45}Ca^{2+}$ measured by a lanthanum method (van Breemen, Farinas, Gerba & McNaughton, 1972) are significantly reduced by Cd^{2+} (Toda, 1976a).

In canine isolated mesenteric arteries, ID_{50}s of verapamil and papaverine against Ca^{2+} contractions were 0.14 and 12 μM respectively, and such data are consistent with the results obtained with rat isolated aortic ring preparations (Massingham, 1973). Contractile responses to Ca^{2+} of cerebral and peripheral arteries of approximately the same size were suppressed in a different manner by vasodilator agents: susceptibility to Cd^{2+} and verapamil was, cerebral > coronary > mesenteric, while that to papaverine was, cerebral = coronary > mesenteric. In contrast to the fact that isoproterenol, acetylcholine (Toda, 1974a) and dopamine (Toda, 1976b) which selectively stimulate respective drug receptors, cause considerably less relaxation in cerebral arteries than in mesenteric and coronary arteries, vasodilator agents acting directly on vascular smooth muscles appear to cause a greater relaxation in cerebral arteries.

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