INTERACTIONS OF Cd++ AND CYSTEINE ON Ca++ CONTENT AND CONTRACTILITY OF ISOLATED AORTAS AND CARDIAC MUSCLES

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Abstract - In isolated rabbit aortas, ventricles and left atria, the addition of Cd++ (0.5 mM) caused a decrease in the content of Ca++ and an increase in the Cd++ content. Contents of Mg++ and Zn++ were not significantly altered. Cysteine (1 mM) applied simultaneously with Cd++ prevented the Ca+-depleting action and also the accumulation of Cd++. Treatment of the tissues with Ca++-free media, EGTA (5 mM) and EDTA (5 mM) also reduced the content of Ca++. Treatment with Cd++ and EGTA did not significantly alter the extracellular space measured with ^14C-inulin. The contractile response of aortic strips to noradrenaline and K+ was abolished by 0.5 mM Cd++. This inhibition was completely prevented by cysteine (1 mM) when noradrenaline was used as a stimulant, and partially prevented when K+ was used. Aortic contractions induced by noradrenaline and K+ were also attenuated by removal of Ca++ from bathing media and EGTA, the attenuation of the response to the ion being greater than that with the amine. Contractions of left atria driven electrically were abolished by 0.5 mM Cd++. Cysteine prevented only partially the inhibitory effect of Cd++. It may be concluded that Cd++ binds SH groups of membrane constituents to prevent influxes of Ca++, thus decreasing the content of Ca++ and reducing the reactivity of aortas and the contractility of atria.

It has been demonstrated that Cd++ applied in situ and in vitro reduces the reactivity of vascular smooth muscles to vasoconstricting agents (1-5) and the contractility of atrial and ventricular myocardium (6-8). This inhibitory effect has been postulated to derive mainly from an interference with inward movements of Ca++ across cell membranes, since Ca+-induced contractions in isolated aortas soaked in Ca++-free media and depolarized by K+ are diminished by treatment with Cd++ (5). This mechanism of action may be reflected by a decrease in the content of Ca++ in these muscles, which in turn results in a further suppression of muscle contractions. Inhibition of the vascular and cardiac contractility by Cd++ is reversed by thiol compounds more effectively than by Ca++ (5, 8).

The aim of the present study was to determine whether or not Cd++ altered the content of divalent cations, such as Ca++, Mg++, Zn++ and Cd++, in aortas, ventricles and left atria isolated from rabbits, to investigate interactions between Cd++ and cysteine on the tissue ion content, and to correlate changes in the ionic content with the reactivity of aortas and the contractility of atria.
MATERIALS AND METHODS

Albino rabbits of both sexes, weighing 1.8 to 2.3 kg, were used. Under ether anesthesia, the animals were sacrificed by exsanguination from common carotid arteries. The heart and the descending aorta (up to diaphragm) were isolated. The aorta was helically cut into strips of approx. 5 x 25 mm. The aortic strip was vertically fixed between hooks under a resting tension of 2 g in a muscle bath of 20 ml capacity containing the nutrient solution. The solution was maintained at 37 ± 0.5°C and gassed with a mixture of 95% O2 and 5% CO2. The hook anchoring the upper end of the strip was connected to the lever arm of a force-displacement transducer (Nihonkoden Kogyo Co., Tokyo). Ventricles and atria were separated, and left atrial preparations were prepared as described in an earlier report (9). The atrial preparations were vertically fixed between hooks under a resting tension of 300 to 400 mg in a muscle bath. The bathing solution was maintained at 30 ± 0.5°C and bubbled with a gas mixture. The pH of the solution was 7.2 to 7.3. The composition of the solution was as follows (mM): Na+, 162.1; K+, 5.4; Ca++, 2.2; Cl-, 157.0; HCO3-, 14.9; dextrose, 5.6. The preparations were equilibrated for 60 min in control media, during which time the bathing medium was replaced twice.

Assay of the ionic content. After the equilibration for 60 min in control solutions, aortic strips, ventricles and left atria were soaked for 30 min in bathing media containing: (1) normal ion composition only (control), (2) 0.5 mM Cd++, (3) 0.5 mM Cd++ and 1 mM cysteine, (4) 1 mM cysteine added 20 min after the addition of 0.5 mM Cd++ (thus exposing preparations for 30 min to Cd++ and for 10 min to cysteine), (5) 1 mM cysteine, (6) no Ca++, (7) 5 mM EGTA and (8) 5 mM EDTA. The preparations thus treated were removed, washed with fresh fluid, blotted and weighed. Then the tissues were digested to a nearly colourless solution with nitric acid, and digestion was completed with perchloric acid to yield a colourless solution. Total volume of the solution was adjusted to 10 (for aortas and atria) or 20 ml (for ventricles) with distilled water, and the amount of Ca++, Mg++, Zn++ and Cd++ was determined by a Shimazu type AA50 atomic absorption spectrophotometer. In the case of Ca++ determination, Sr++ (2 mg/ml final concentration) was added to eliminate interference with other cations and anions (10).

Assay of inulin space. Small pieces of aortas, ventricles and left atria weighing 10 to 15 mg were incubated at 37 ± 0.5°C in 1 ml bathing media containing 1 μCi 14C-inulin. During the incubation period, the medium was bubbled with a gas mixture. Cd++ (0.5 mM) or EGTA (5 mM) was added to the medium at the beginning of experiments. The tissues were removed, blotted, weighed and transferred to counting vials, to which 3 ml of NCS solution (Nuclear Chicago) were added. The vials were incubated at 50°C until the solid dissolved. Ten milliliters of toluene containing 8 g PPO (2,5-diphenyloxazole) and 130 mg dimethyl POPOP (1,4-bis[2-(4-methyl-5-phenyloxazolyl)] benzene) per liter were then added. Samples were counted for radioactivity using a liquid scintillation counter (Nuclear Chicago, Mark II). The external standard channels ratio method was used to correct the quenching. Counting efficiency was about 70%.

Reactivity of aortic strips to stimulatory agents. Seven pieces of aortic strips from the
same rabbits were prepared. After equilibration for 60 min, the preparations were treated for 30 min with the media shown above as (1) to (7). After the end of the treatment, noradrenaline or K+ were added directly to the media to give final concentrations of $2 \times 10^{-8}$ M and 30 mM, respectively. The amine and the ion at these concentrations produced a 70 to 85% maximum contraction. In Cd++-treated preparations, 1 mM cysteine was added after the maximum response to noradrenaline or K+ had been attained. In preparations treated with Ca++-free media and with 5 mM EGTA, Ca++ in concentrations of 2.2 mM (normal [Ca++]o) and 5 mM, respectively, was added after the maximum response to the agents had been attained.

**Contractility of left atria.** Left atrial preparations were driven electrically by square pulses of supramaximal intensity (about 4 mA) with a 2 msec duration at a frequency of 60/min. Stimulating bipolar electrodes were placed close to the cut end of the atria. Electrical stimuli were provided by an electronic stimulator (type SEN 1101, Nihonkoden Kogyo Co.). After 60 min exposure to control media, Cd++ (0.5 mM), cysteine (1 mM), Cd++ plus cysteine, or EGTA (5 mM) was added. Contractions before the addition of these agents and after 30 min exposure were compared.

Drugs used were dl-noradrenaline hydrochloride, L-cysteine hydrochloride, ethylene glycol-bis-(β-aminomethyl ether)-N,N′-tetraacetic acid (EGTA, dissolved in 1 N NaOH) and ethylenediamine tetraacetic acid disodium salt (EDTA). Results shown in the text and tables represent mean values ± standard errors of the means. Significance of difference between means was estimated by Student’s t test.

**RESULTS**

**Effects of Cd++ and cysteine on the content of divalent cations**

Contents of Ca++, Mg++, Zn++ and Cd++ in isolated aortas, ventricles and left atria from rabbits are illustrated in Tables 1, 2 and 3.

**TABLE 1. Contents of divalent cations in isolated aortas treated with Cd++, cysteine, Ca++-free media, EGTA and EDTA**

| Treatment                          | N  | Contents (mmoles/kg wet tissue) of |          |          |          |          |
|-----------------------------------|----|-----------------------------------|----------|----------|----------|----------|
|                                   |    | Ca++                             | Mg++     | Zn++     | Cd++     |          |
| None                              | 22 | 2.53±0.12                       | 2.18±0.16| 0.27±0.02|          |          |
| Cd++ 0.5 mM                       | 14 | 1.81±0.13                      | 1.73±0.20| 0.44±0.13| 0.83±0.13|          |
| Cd++ 0.5 mM+cysteine 1 mM         | 11 | 2.13±0.19                       | 2.03±0.27| 0.24±0.01| 0.22±0.02|          |
| Cd++ 0.5 mM then cysteine 1 mM*   |  6 | 2.80±0.34                       | 2.62±0.21| 0.40±0.08| 0.56±0.06|          |
| Cysteine 1 mM                     | 12 | 2.53±0.19                       | 2.73±0.32| 0.31±0.03|          |          |
| Ca++-free media                   |  6 | 1.80±0.13                       | 2.64±0.41| 0.24±0.02|          |          |
| EGTA 5 mM                         | 13 | 1.24±0.11                       | 1.81±0.22| 0.25±0.03|          |          |
| EDTA 5 mM                         |  5 | 1.47±0.48                       | 1.57±0.21| 0.28±0.04|          |          |

* Cysteine was added after 20 min exposure to Cd++.  
a, significant difference from control, P<0.001. b, P<0.01.  
N, number of preparations used.  
., not detected.
TABLE 2. Contents of divalent cations in isolated ventricles treated with Cd++, cysteine, Ca++-free media, EGTA and EDTA

| Treatment                      | N  | Ca++   | Mg++  | Zn++  | Cd++   |
|-------------------------------|----|--------|-------|-------|--------|
| None                          | 33 | 1.72±0.05 | 4.78±0.12 | 0.32±0.01 | --     |
| Cd++ 0.5 mM                   | 20 | 1.30±0.06a | 4.74±0.19 | 0.35±0.02 | 0.20±0.03 |
| Cd++ 0.5 mM + cysteine 1 mM   | 15 | 1.74±0.05 | 5.65±0.23 | 0.30±0.01 | 0.08±0.01 |
| Cd++ 0.5 mM then cysteine 1 mM | 9  | 1.44±0.10b | 5.08±0.39 | 0.31±0.01 | 0.11±0.02 |
| Cysteine 1 mM                 | 16 | 1.76±0.20 | 5.79±0.78 | 0.32±0.02 | --     |
| Ca++-free media               | 6  | 1.53±0.07 | 4.64±0.08 | 0.28±0.01 | --     |
| EGTA 5 mM                     | 11 | 1.36±0.06a | 5.24±0.31 | 0.32±0.01 | --     |
| EDTA 5 mM                     | 7  | 1.02±0.19a | 4.90±0.16 | 0.29±0.01 | --     |

* Cysteine was added after the 20 min exposure to Cd++. a, significant difference from control, P<0.001. b, P<0.05.
N, number of preparations used.
-, not detected.

In isolated aortas, the addition of Cd++ in a concentration of 0.5 mM to the bathing medium caused a significant decrease in the content of Ca++ and an increase in the Cd++ content (Table 1). Tissue Mg++ and Zn++ were not significantly influenced. Cysteine (1 mM) applied simultaneously with Cd++ or after 20 min exposure to Cd++ prevented and reversed the effect of Cd++ on the tissue Ca++, and also reduced the accumulation of Cd++ in the tissue. Difference in the Cd++ content in preparations treated with Cd++ alone and with Cd++ plus cysteine is significant (P<0.001). Cysteine by itself did not influence contents of the divalent ions measured. Treatment of aortas for 30 min with Ca++-free media, EGTA and EDTA decreased the tissue Ca++, but did not significantly alter the content of Mg++ and Zn++.

Treatment of ventricles for 30 min with 0.5 mM Cd++ decreased the content of Ca++ and increased the content of Cd++ (Table 2). Cysteine (1 mM) applied simultaneously with Cd++ antagonized the Cd++-induced reduction in the tissue Ca++, but the thiol compound when added after 20 min exposure to Cd++ failed to reverse the effect of Cd++. Accumulation of Cd++ in the tissues was reduced by cysteine. Difference in the content of...
Cd** in preparations treated with Cd** alone and with Cd** plus cysteine is significant (P<0.01). Contents of divalent ions measured were not significantly altered by treatment with 1 mM cysteine alone. Exposure of preparations for 30 min to Ca**-free media, EGTA and EDTA decreased the tissue Ca**.

Treatment of left atria with 0.5 mM Cd** tended to decrease the tissue Ca** (Table 3). Cysteine (1 mM) antagonized the effect of Cd**. Contents of Cd** in preparations treated with Cd** alone and with Cd** plus cysteine were significantly different (P<0.05).

**Inulin space of aortas, ventricles and left atria treated with Cd****

**14C-Inulin was rapidly accumulated in aortas, ventricles and atria during the first 30 min exposure and the accumulation curve levelled off after a 60 min exposure. The extracellular space thus measured in these preparations was not significantly altered by treatment for 30 and 60 min with 0.5 mM Cd** or with 5 mM EGTA. The results are summarized in Table 4.

| Tissue       | Treatment | Inulin space (% of wet weight) | Inulin space (% of wet weight) |
|--------------|-----------|-------------------------------|-------------------------------|
|              |           | 30 min*                        | 60 min                        |
|              | N         |                               |                               |
| Aorta        | None      | 7 50±2                        | 7 53±11                       |
|              | Cd** 0.5 mM | 8 43±3                       | 8 50±5                        |
|              | EGTA 5 mM  | 7 49±4                       | 8 66±9                        |
| Ventricle    | None      | 8 37±2                       | 8 47±4                        |
|              | Cd** 0.5 mM | 8 38±2                       | 7 48±3                        |
|              | EGTA 5 mM  | 7 35±3                       | 8 45±5                        |
| Left atrium  | None      | 8 37±3                       | 5 45±1                        |
|              | Cd** 0.5 mM | 8 31±2                       | 7 39±3                        |
|              | EGTA 5 mM  | 8 42±6                       | 7 45±4                        |

N, number of preparations used.
* time of exposure to experimental solution.

**Changes in the contractility of aortas and left atria by Cd**** and cysteine**

The contractile response of helically cut strips of rabbit aortas to noradrenaline (2×10^{-5} M) was almost completely abolished by treatment for 30 min with Cd** (0.5 mM). In these preparations, the addition of cysteine at 1 mM caused contraction (Fig. 1); sum of the maximum contraction induced by cysteine (0.54 g) and by noradrenaline (0.10 g) in the presence of Cd** being approximately 31 % that by noradrenaline in control preparations and preparations treated with cysteine or with Cd** plus cysteine. Cysteine (1 mM) applied simultaneously with Cd** completely prevented the inhibitory effect of Cd** (Fig. 1). When cysteine was added after 20 min exposure to Cd**, the inhibition of the response to noradrenaline by Cd** was partially reversed. In control preparations, cysteine did not produce contractions nor influence the response to noradrenaline. When the preparations had contracted with noradrenaline, cysteine rather produced relaxation.
Fig. 1. Contractile response of aortic strips to noradrenaline in preparations treated for 30 min with 1 mM cysteine, 0.5 mM Cd++, and with a combination of cysteine and Cd+++. Concentrations of noradrenaline and Ca++: 2×10⁻⁶ M and 4.4 mM, respectively. Strips were obtained from the same rabbit.

(0.24±0.06 g, N=3). Treatment of aortic strips for 30 min with Ca++-free media or 5 mM EGTA significantly reduced the contractile response to noradrenaline: greater reduction of the response was observed with EGTA treatment. The results are summarized in Table 5.

Contractile responses to K⁺ (30 mM) were completely abolished by 0.5 mM Cd++ and 5 mM EGTA, and moderately reduced by exposure for 30 min to Ca++-free media (Table 5). Cysteine partially prevented and reversed the inhibitory effect of Cd++.

Contractions of left atria driven electrically were completely abolished by treatment for 30 min with 0.5 mM Cd++. The inhibitory effect of Cd++ was partially antagonized by 1 mM cysteine applied simultaneously with Cd++. However, when contractions were once abolished by 0.5 mM Cd++, cysteine failed to restore the mechanical activity. Treatment with EGTA (5 mM) almost completely abolished atrial contractions and generated spontaneity. The results are tabulated in Table 6.
TABLE 5. Contractile responses of aortic strips to noradrenaline and K⁺ in preparations treated with Cd⁺⁺, cysteine, Ca⁺⁺-free media and EGTA

| Treatment | Contractile response to Noradrenaline (g) | Contractile response to K⁺ (g) |
|-----------|------------------------------------------|-------------------------------|
| None      | N=11                                      | N=8                           |
| Cysteine 1 mM | N=11                                      | N=8                           |
| Cd⁺⁺ 0.5 mM | N=11                                      | N=8                           |
| + cysteine 1 mM* | N=7                                       | N=6                           |
| Cd⁺⁺ 0.5 mM + cysteine 1 mM | N=11                                      | N=8                           |
| Cd⁺⁺ 0.5 mM then cysteine 1 mM** | N=11                                      | N=8                           |
| Ca⁺⁺-free media | N=11                                      | N=8                           |
| + Ca⁺⁺ 2.2 mM* | N=10                                      | N=8                           |
| EGTA 5 mM | N=11                                      | N=8                           |

* Responses to cysteine or Ca⁺⁺ added after the maximum contraction induced by noradrenaline and K⁺ was attained.
** Cysteine was added after 20 min exposure to Cd⁺⁺.
N, number of preparations used.
a, significant difference from control, P<0.001. b, P<0.05.
Figures in parentheses indicate percent changes from control.

TABLE 6. Modification of atrial contractions by Cd⁺⁺, cysteine and EGTA

| Treatment | N | Atrial contraction (mg) |
|-----------|---|-------------------------|
| None      | 7 | 759±86                  |
| Cysteine 1 mM | 7 | 736±73                  |

None

| Treatment | N | Atrial contraction (mg) |
|-----------|---|-------------------------|
| Cd⁺⁺ 0.5 mM | 5 | 464±50                  |

| Treatment | N | Atrial contraction (mg) |
|-----------|---|-------------------------|
| None      | 6 | 768±109                 |
| Cd⁺⁺ 0.5 mM + cysteine 1 mM | 6 | 427±91b                 |

| Treatment | N | Atrial contraction (mg) |
|-----------|---|-------------------------|
| None      | 6 | 473±55                  |
| EGTA 5 mM | 6 | 36±18a                  |

N, number of preparations used.
a, significant difference from control, P<0.001. b, P<0.05.
Figures in parentheses indicate percent changes from control.

DISCUSSION

Results obtained from tissue Ca⁺⁺ measurement show that treatment of aortas, ventricles and left atria with 0.5 mM Cd⁺⁺ reduce cellular Ca⁺⁺ concentrations. This reduction in the tissue Ca⁺⁺ could result from decreased Ca⁺⁺ uptake, increased Ca⁺⁺ release,
or both. Because of the findings that Ca\(^{++}\)-induced contractures of isolated rabbit aortas exposed to Ca\(^{++}\)-free media and depolarized by K\(^{+}\) are suppressed by prior treatment with Cd\(^{++}\) (5), a decrease in the Ca\(^{++}\) uptake is more likely. With La\(^{+++}\), similar reduction in the tissue Ca\(^{++}\) and in the vascular reactivity to stimulating agents has been observed (11, 12). La\(^{+++}\) is postulated to replace Ca\(^{++}\) at superficial or extracellular binding sites and subsequently prevent uptake or binding of Ca\(^{++}\) at various cellular sites or stores (13–15). This mechanism of action of La\(^{+++}\) is supported by the following: La\(^{+++}\) and Ca\(^{++}\) have roughly the same hydrated radii and the high valence of La\(^{+++}\) will cause it to bind more strongly to Ca\(^{++}\) binding sites (16), La\(^{+++}\) induces rapid \(^{41}\)Ca\(^{++}\) loss from rabbit aortas, which is virtually the same as the La\(^{+++}\)-induced \(^{41}\)Ca\(^{++}\) loss from acellular rabbit tendon (14), efflux of \(^{41}\)Ca\(^{++}\) from guinea pig ileum is transiently increased by La\(^{+++}\) only in muscles previously exposed to Ca\(^{++}\)-free media during washout (13), and La\(^{+++}\) is poorly transported across cell membranes (17, 18). Cd\(^{++}\) has been shown to interact with cellular constituents containing SH groups (19), and effects of Cd\(^{++}\), but not those of La\(^{+++}\), were prevented and reversed by cysteine and other thiol compounds (present study and 5, 8), suggesting an involvement of cellular SH groups in Cd\(^{++}\)-induced changes in tissue Ca\(^{++}\) and muscle contractility. Since there are no data to support the fact that Cd\(^{++}\) shares cellular SH groups as binding sites with Ca\(^{++}\), it seems unlikely that replacement of Ca\(^{++}\) with Cd\(^{++}\) is the mechanism underlying the Ca\(^{++}\)-depleting action of Cd\(^{++}\). To analyze further the mechanism of actions of Cd\(^{++}\), study with \(^{41}\)Ca\(^{++}\) is underway.

Decrease in the content of Ca\(^{++}\) by Cd\(^{++}\) was prevented and partially reversed by cysteine. Accumulation of Cd\(^{++}\) in tissues was also significantly attenuated by cysteine. Mean values of Cd\(^{++}\) determined in aortas and left atria soaked in media containing both Cd\(^{++}\) and cysteine (0.22 and 0.23 mmol/kg wet tissue, respectively) were roughly the amount of Cd\(^{++}\) present in extracellular space, because the concentration of Cd\(^{++}\) in bathing media was 0.5 mM and extracellular space in these tissues was calculated as roughly 50 and 40%, respectively. Thus, 0.61 (0.83 minus 0.22, Table 1) and 0.22 (0.45 minus 0.23, Table 3) mmol/kg wet tissue can be estimated as the amount accumulated in muscle cells during a 30 min incubation. Isolated rabbit aortas exposed for 8 min to \(10^{-6}\) M Cd\(^{++}\) have been demonstrated to bind the ion in 0.04 mmol/kg dry tissue (20). A smaller amount of accumulation of Cd\(^{++}\) in ventricles may be due to an insufficient incubation period for such thick tissue. That cysteine when applied simultaneously with Cd\(^{++}\) prevents both accumulation of Cd\(^{++}\) and reduction of tissue Ca\(^{++}\) suggests that the reduction of Ca\(^{++}\) is associated with Cd\(^{++}\) accumulation. These findings support the idea that Cd\(^{++}\) binds SH groups of membrane constituents to prevent the uptake of Ca\(^{++}\) by muscle cells (5). The dithiol-binding ion appears to have a greater affinity for cysteine than for SH groups of aortic and atrial muscles.

Attenuation of the contractile response of aortic strips to K\(^{+}\) by removal of Ca\(^{++}\) from bathing media was apparently greater than that with noradrenaline, suggesting that contractions induced by K\(^{+}\) are mainly associated with increased Ca\(^{++}\) influx, while those induced by noradrenaline are associated with increments in the influx of Ca\(^{++}\) and the re-
lease of Ca\textsuperscript{2+} from intracellular stored sites. At low concentrations of Cd\textsuperscript{2+} (0.02 and 0.1 mM), K\textsuperscript{+}-induced contraction was reduced more markedly than that induced by noradrenaline; thus, it was postulated that Ca\textsuperscript{2+} influx is preferentially blocked by Cd\textsuperscript{2+} (5). However, at the concentration used in the present study (0.5 mM.), the response to noradrenaline was almost completely suppressed as was the response to K\textsuperscript{+}. This could be due to diminished influxes of Ca\textsuperscript{2+} and also decreased cellular Ca\textsuperscript{2+} available for contraction in response to noradrenaline. Cysteine restores the vascular response, possibly by removing Cd\textsuperscript{2+} from binding sites in membranes, thus permitting more Ca\textsuperscript{2+} to enter and act on contractile proteins as well as to replenish stored sites.

Atrial contractions were completely abolished by treatment for 30 min with 0.5 mM Cd\textsuperscript{2+}, and cysteine even though applied simultaneously with Cd\textsuperscript{2+} prevented only partially the inhibitory effect of Cd\textsuperscript{2+}. Decrease in the content of Ca\textsuperscript{2+} and accumulation of Cd\textsuperscript{2+} in atrial preparations treated with Cd\textsuperscript{2+} were antagonized by cysteine. This discrepancy may derive from the fact that the contractility of atrial preparations is extremely sensitive to Cd\textsuperscript{2+} as this ion at 0.005 mM is already effective in decreasing contractions and at 0.02 mM reduces contractions (developed at a driving frequency of 60/min) to approx. 1/3 those of control (8).

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