Short communication

Paradoxical Effects of La^{3+} on the Na^+-loaded Ureter and Taenia Coli Smooth Muscles of the Guinea Pig

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La^{3+} is known to antagonize Ca^{2+} movement across the cell membrane (van Breemen et al. 1973; Langer and Frank 1972; Sarkadi et al. 1977).

However, recently Mead and Clusin (1985) reported on the paradoxical effect of La^{3+} on chick embryonic cardiac cells. They found that La^{3+} potentiated low-Na^+ contracture and accentuated local contractions seen in Na^+-free solution which are thought to reflect Ca^{2+}-induced Ca release in heart muscle (Eisner et al. 1985).

In the present study we also present some evidence on the paradoxical effects of La^{3+} on the Na^+-loaded ureter and taenia coli smooth muscles.

Tension alone was recorded with the continuous superfusion technique described in detail by Brading and Sneddon (1980).

A modified Krebs solution of the following composition was used (mmol/l): Na^+, 120.3; K^+, 5.9; $Tris^+$, 16.6; Ca^{2+}, 2.5; Mg^{2+}, 1.2; Cl^-, 150.2; glucose, 11.5; equilibrated with 100% O_2, pH 7.4. Na-free solutions were made by replacing Na^+ isoosmotically with K^+ or $Tris^+$. Na-loading of the tissue was done by exposing the muscle to ouabain (10^{-4} mol/l) for 60 min.

Electrophysiological experiments showed that La^{3+} (0.2—1 mmol/l) blocked the evoked action potential preferentially blocking the spike component and phasic contraction as well as the high-K^+ contracture of ureter muscle. Also, only in high concentrations (5—10 mmol/l) La^{3+}, when applied before Na_0^+-withdrawal suppressed Na^+free contracture of Na^+-loaded ureter muscle. All these findings reflect the Ca^{2+} antagonistic action of La^{3+} which could be best explained if La^{3+} replaced Ca^{2+} on superficial binding sites as was found previously (van Breemen et al. 1973).

On the other hand, we found that application of La^{3+} even in high concentrations (5—10 mmol/l) during development of the tonic component of the

Na^+-free contracture of the Na^+-loaded ureter muscle caused further elevation of muscle tone irrespective of the Na^+ substitute used (Fig. 1, I*Ab*, *Bb*). This was typical only for the Na^+-loaded tissue, since application of La^{3+} during the development of tonic component of high-K^+ (126 mmol/l K^+) contracture of normal tissue produced relaxation (Fig. 1, I*Cb*). However, in all cases La^{3+} (5 mmol/l) strongly potentiated caffeine (20 mmol/l) contractures (Fig. 1). It was found that both Na^+-loaded and normal tissue in the presence of La^{3+} in Na^+-containing solution, were able to develop caffeine contractures which in fact were smaller in amplitude than the ones seen in Na^+-free solution (Fig. 1).

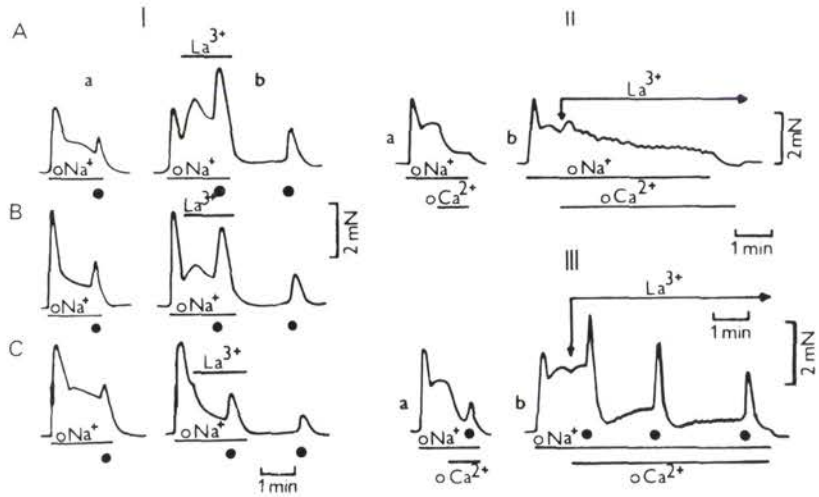

Fig. 1. Effects of La^{3+} (5 mmol/l) on the Na^+-free and caffeine (20 mmol/l) contractures of the Na^+-loaded ureter muscle. (I*a*) Control contractures of Na^+-loaded ureter muscle induced by Na^+-free solution and caffeine with $Tris^+$ (*A*) and K^+ (*B*) used as Na^+ substitutes, and 126 mmol/l K^+ (*C*) induced contracture of normal tissue. (I*b*) Changes in muscle tone and caffeine responses obtained after addition of La^{3+} (5 mmol/l) in the course of development of the Na^+-free (*A*, *B*) and high-K^+ (*C*) contracture. (II*A*) Relaxation of tonic component of the Na^+-free ($Tris^+$ substitution) contracture induced by Ca^{2+}-free (3 mmol/l EGTA) solution. (II, *B*) Persistence of tonic tension and appearance of small fluctuations of tension in Na^+, Ca^{2+}-free solution caused by addition of La^{3+} (5 mmol/l). (III, *A*) Relaxation of tonic component of the Na^+-free contracture and caffeine response obtained in Na^+, Ca^{2+}-free solution with 3 mmol/l EGTA added. (III, *B*) Potentiation and persistence of caffeine contractures caused by addition of La^{3+} (5 mmol/l) to Na^+, Ca^{2+}-free solution. Caffeine application for 20 s is marked by filled circles.

It was found that La^{3+} (5 mmol/l) prevented relaxation of the tonic component of the Na^+-free contracture normally seen upon withdrawal of Ca^{2+} from the bathing fluid (Fig. 1, II*A*). Fig. 1, II*B* shows that the muscle did not relax and

small fluctuations of the tonic tension were normally seen in Na^+, Ca^{2+}-free solution with 5 mmol/l La^{3+}. Also, it was found that under these conditions ureter muscle was able to generate full sized transient contractures to repetitive applications of caffeine (20 mmol/l) (Fig. 1, III*B*).

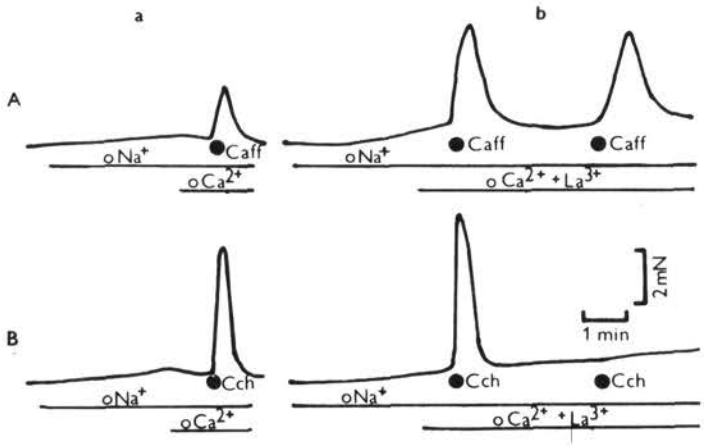

Fig. 2. Effects of La^{3+} (5 mmol/l) on caffeine (20 mmol/l) and carbachol (10^{-4} mol/l) responses of the Na^+-loaded taenia coli. Contractures induced by caffeine (*A*) and carbachol (*B*) applied to Na^+, Ca^{2+}-free solution in the absence (*Aa, Ba*) and presence (*Ab, Bb*) of 5 mmol/l La^{3+} added to Na^+, Ca^{2+}-free solution. Records from individual tissues. Note small rise in tonic tension caused by Na^+-free solution. Caffeine and carbachol were applied for 20 s (filled circles).

La^{3+} (5 mmol/l) also potentiated both carbachol and caffeine contractures of Na^+-loaded taenia coli (Fig. 2*Ab, Bb*). Again, caffeine could cause repetitive contractions of the Na^+-loaded taenia placed in Na^+, Ca^{2+}-free solution with 5 mmol/l La^{3+} (Fig. 2, *Ab*). Contrary to caffeine, carbachol could cause only a single full sized contracture under these conditions (Fig. 2, *Bb*). The paradoxical effects of La^{3+} seen in our experiments could best be explained if we suggest that La^{3+} blocks a Na^+ independent Ca^{2+} extrusion system which is likely to be an ATP-driven Ca^{2+} pump similar to that found in red blood cell which in fact was exquisitely inhibited by externally applied La^{3+} (Sarkadi et al. 1977).

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