Short communication

Effects of Quinidine on the Electrical Activity and Contractile Responses of the Guinea-Pig Ureter Smooth Muscle

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Quinidine and its stereoisomere quinine suppress various membrane conductances in a variety of cells (Ducouret 1976; Yeh and Narahashi 1976; Nawrath 1981; Lee et al. 1981; Hermann and Gorman 1984). Recently quinidine has been classified as a putative blocker of the Na-Ca exchange in heart muscle (Mentrard et al. 1984; Chapman et al. 1984).

The effects of quinidine on the contractile responses of the ureter muscle of the guinea-pig associated with both the entry of Ca via voltage-operated Ca channels and the Na-Ca exchange operating in Na-loaded ureter in Na-free solutions (Aickin et al. 1984) were studied and low-Na contracture was observed in the latter case. The present experiments were performed on isolated segments of whole ureter using the double sucrose-gap method for simultaneous recording of electrical and mechanical activity (Bülbring and Tomita 1969) and the superfusion technique for tension recording (Brading and Sneddon 1980).

The composition of the Krebs solution was (in mmol/l): Na^+ 136.9; K^+ 5.9; Ca^{2+} 2.5; Mg^{2+} 1.2; Cl^- 133.5; $H_2PO_4^-$ 1.2; HCO_3^- 15.5; glucose 11.5, bubbled with 97 % O_2 + 3 % CO_2 at 36—37 °C.

Loading of the tissue with Na ions was produced through inhibition of the Na-K pump by treatment of the ureter with ouabain as described ealier (Aickin et al. 1984).

Fig. 1 shows the effects of quinidine on the evoked action potentials, phasic contractions and potassium contracture (126 mmol/l − K^+). Fig. 1*A* shows that 10^{-4} mol/l quinidine caused a shortening of the plateau component of the action potential and a small decrease in the amplitude of the spike component (Fig. 1*A*, b, c). Simultaneously, the amplitude of the phasic contraction was decreased. The effects of quinidine on the action potential and phasic contraction were reversible (Fig. 1*A*, d). The dose-response curve of the inhibition of the phasic contractions by quinidine is shown in Fig. 1*C* (curve b). Quinidine caused a dose-dependent

inhibition of potassium contracture with predominant action on the tonic component (Fig. 1*B*). The dose-response curve of quinidine-induced inhibition of the tonic component of potassium contracture of ureter muscle is illustrated in Fig. 1*C* (curve a). Fig. 1*C* shows that quinidine selectively blocks the tonic component of the potassium contracture at 5×10^{-5} mol/l, a concentration which had no effect on action potential associated phasic contractions (Fig. 1*C*, curve b). These results favour the idea concerning the existence of several populations of voltage-operated Ca channels in ureter muscle (Kochemasova and Shuba 1979; Brading et al. 1983). The effects of quinidine are qualitatively similar to those induced by organic Ca blockers (Aickin et al. 1984). However, unlike the latters, quinidine was found to have a significant inhibitory action on low-Na contractures.

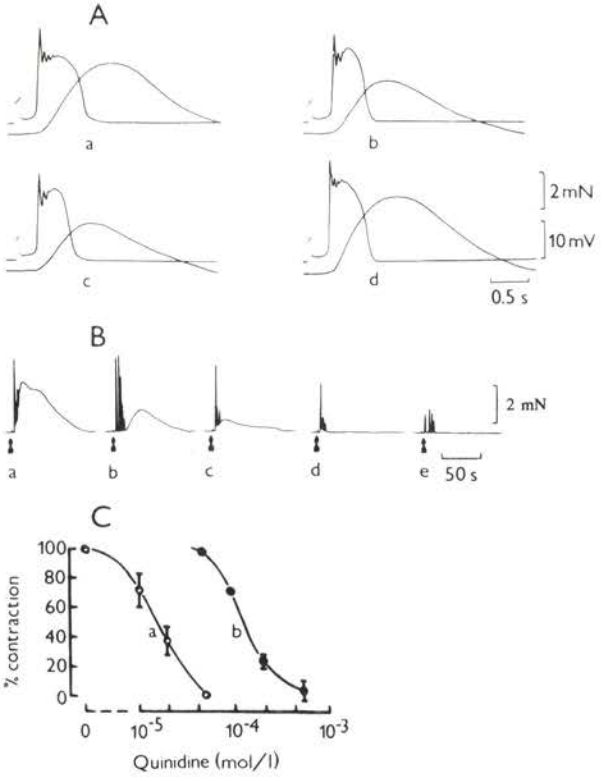

Fig. 1. Effects of quinidine on the ureter smooth muscle (the double sucrose-gap method). *A*, effect of quinidine (10^{-4} mol/l) on the evoked action potentials (upper trace) and phasic contractions (lower trace). *A*, a, control; *A*, b, c, during exposure to quinidine for 2 and 5 min; *A*, d, after washout with Krebs solution for 5 min. *B*, effects of quinidine on high-K contracture; *B*, a, control; *B*, b, c, d, e, during exposure to quinidine at 10^{-5}, 2×10^{-5}, 5×10^{-5} and 10^{-4} mol/l, respectively (arrows indicate the administration of KCl). *C*, dose-response curves or the inhibition of tonic (a) and phasic (b) contractions of the ureter muscle by quinidine.

Fig. 2*A* shows a typical contractile response of Na-loaded ureter muscle upon replacement of all Na^+ by $Tris^+$ (low-Na contracture), and an enhancement of this contracture by further replacement of $Tris^+$ by K^+ regardless of the constant presence of nifedipine (10^{-5} mol/l) in the bathing fluid. Nifedipine abolishes the possible enhancement of Ca ions entry via potential-operated Ca channels, which are normally activated by high-K depolarization. The enhancement of low-Na contracture in high-K solution suggests an electrogenic mode of operation of the Na-Ca exchange. The value of the resting membrane potential of the Na-loaded ureter smooth muscle in Krebs solution is about −57 mV and close to 0 mV in high-K (126 mmol/l) solution. Fig. 2*B* shows the effect of quinidine at 0.5 mmol/l on low-Na contracture. It is evident from Fig. 2*B* that quinidine caused a reduction in the contractile response by 60—70 % with either substitute used. A complete inhibition of the low-Na contracture was never seen in our experiments in the concentration range studied. The effect of quinidine on the low-Na contracture was reversible (Fig. 2*C*). Caffeine contracture normally seen in Ca-free solution was resistant to quinidine.

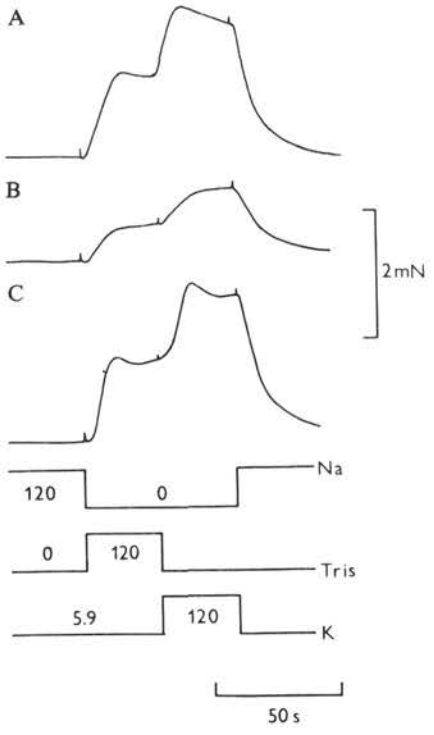

Fig. 2. Effect of quinidine on low-Na contracture in the presence of nifedipine (10^{-5} mol/l) (tension recording). *A*, low-Na contracture of Na-loaded ureter upon replacement of Na^+ by $Tris^+$ and enhancement of this contracture by further substitution of $Tris^+$ for K^+, *B*, during exposure to 0.5 mmol/l quinidine for 5 min; *C*, recovery of the low-Na contracture in 10 min after removal of quinidine from the bathing fluid.

The results obtained suggest that, at least in ureter muscle, quinidine at low concentrations ($10^{-5} - 10^{-4}$ mol/l) acts mainly as a blocker of noninactivating potential-operated Ca channels opened during sustained deplarization. At higher concentrations (0.2—0.5 mmol/l) inhibitory effects of quinidine on the Na/Ca channels responsible for the plateau phase of the action potential and on voltage-sensitive Na-Ca exchange were also observed.

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