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Stereoselective effects of the enantiomers, quinidine and quinine, on depolarization- and agonist-mediated responses in rat isolated aorta

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1 The effects of the two enantiomers, quinidine and quinine, were studied on depolarization- and agonist-induced isometric contractions in rat isolated thoracic aortic rings.

2 Quinidine or quinine (10^{-6}M–3×10^{-4}M) produced a concentration-dependent relaxation of 80 mM KCl-contracted rings, the pD_2 values being 4.89 and 4.23, respectively. Thus, quinidine was about 4–5 times more potent than quinine.

3 The voltage-dependence of quinidine- and quinine-induced inhibition was studied in rings that had been incubated in 5 or 40 mM KCl Ca^{2+}-free solution and then contracted by changing the bath solution to 100 mM KCl and 2 mM Ca^{2+}. The inhibitory effects of quinidine were significantly enhanced when the rings were preincubated in 40 mM KCl (depolarizing conditions), when compared to normally polarized rings. In contrast, the effects of quinine were similar in 5 or 40 mM KCl solution.

4 The antagonism of noradrenaline (NA)-induced contractions by low concentrations of quinidine ($<10^{-4}$M) and quinine ($<3 \times 10^{-4}$M) was competitive, as demonstrated by the concentration-dependent parallel rightward shift of the NA concentration-response curves (pA_2 values 6.20 and 5.68, respectively, $P<0.05$).

5 At low concentrations ($\leq 3 \times 10^{-5}$M), quinidine and quinine did not shift the concentration-response curve to 5-hydroxytryptamine (5-HT) or endothelin-1, whereas at higher concentrations they produced a downward shift of these curves. Quinidine and quinine ($>10^{-4}$M) inhibited to a similar extent both the phasic (induced in Ca^{2+}-free media) and tonic responses (after restoring extracellular Ca^{2+}) induced by 5-HT.

6 In conclusion, quinidine and quinine produced a stereoselective inhibition of depolarization and NA-induced contractions, quinidine being more potent than quinine. The inhibition of KCl-induced contractions could be attributed to inhibition of Ca^{2+} entry. Both drugs also behaved as competitive antagonists of α_{1D}-adrenoceptors. At high concentrations, quinidine and quinine also decreased the contractions induced by endothelin-1 and 5-HT in a non-stereoselective manner.

Keywords: Quinidine; quinine; Ca^{2+} channel blockers; α_1-adrenoceptors; rat aorta

Introduction

Quinine and its enantiomer, quinidine, are two alkaloids derived from the cinchona bark. Despite their qualitatively similar pharmacological properties, quinidine and quinine exhibit different therapeutic profiles. Quinidine is widely used in supraventricular and ventricular arrhythmias (Nappi & Mason, 1990), whereas quinine which is less potent and less toxic is preferred for the treatment of malaria (White, 1988).

Parenteral administration of therapeutic doses of quinidine and quinine caused forearm vasodilatation and decreased mean arterial blood pressure (Schmid *et al.*, 1974; Bateman & Dyson, 1986; Nappi & Mason, 1990; Mariano *et al.*, 1992). It has been known for over 60 years that quinine and quinidine can attenuate vasoconstrictor responses to sympathetic nerve stimulation and regional noradrenaline (NA) infusion, effects consistent with their postjunctional α-adrenoceptor antagonistic properties (Nelson, 1928; Hiatt, 1950; Schmid *et al.*, 1974; Mecca *et al.*, 1980; Caldwell *et al.*, 1983). In rat cardiac membranes, human platelets and rat kidney, quinidine is a competitive antagonist at α_1- and α_2- receptors, but it is substantially more potent in antagonizing α_1- than α_2-adrenoceptors (Motulsky *et al.*, 1984). However, vasodilatation is still observed when quinidine is infused in denervated extremities, indicating that a non-adrenergic effect is also involved (Nelson *et al.*, 1974; Schmid *et al.*, 1974; Mariano *et al.*, 1992). The exact mechanism responsible for this non-adrenergic effect is not fully understood.

In isolated cardiac preparations quinidine and quinine inhibit Na^+ (Weidmann, 1955; Hondeghem & Matsubara, 1988), Ca^{2+} (Salata & Wasserstrom, 1988; Scamps *et al.*, 1989) and K^+ currents (Colatsky, 1982; Roden *et al.*, 1988; Cook & Quast, 1990). Very recently, it has been reported that several class I antiarrhythmic drugs (e.g. Na^+ channel blockers) such as propafenone (Carrón *et al.*, 1991), flecainide (Pérez-Vizcaíno *et al.*, 1991), quinidine (Pérez-Vizcaíno *et al.*, 1994), imipramine (Fernández del Pozo *et al.*, 1994) and mexiletine (Dohi *et al.*, 1994) inhibited vascular smooth muscle contraction and this effect was accompanied by a decrease in Ca^{2+} entry. Quinine also inhibited the contractions induced by KCl and angiotensin II in rabbit aorta (Cook *et al.*, 1987) and the $^{45}Ca^{2+}$ uptake induced by KCl in A7r5 cells (Cook & Quast, 1990).

Because the vascular effects of quinidine and quinine have not been previously compared, in an attempt to characterize better the mechanisms involved in their vasodilator effects, we have studied the stereoselectivity of the effects of the two enantiomers, quinidine and quinine, on depolarization- and agonist-induced contractions elicited in rat isolated aorta.

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Methods

Tissue preparation

Male Sprague-Dawley rats (300–350 g), obtained from Interfauna S.A. (Barcelona, Spain) were killed by a blow on the head and exsanguinated. The descending thoracic aorta was rapidly dissected and placed in physiological saline solution (PSS) of the following composition (mM): NaCl 118, KCl 5, $NaHCO_3$ 25, $MgSO_4$ 1.2, $CaCl_2$ 2, KH_2PO_4 1.2 and glucose 11 bubbled with 95% O_2-5%CO_2 gas mixture. After excess surrounding tissue had been removed the aortae were cut into rings (3–4 mm in length). The endothelium was mechanically removed by rubbing the internal surface of the vessels with a small metal rod. Arterial rings were mounted in 5 ml organ baths containing PSS under 2 g of resting tension by two parallel L-shaped stainless-steel holders inserted into the lumen. One holder served as anchor and the other was attached to a force-displacement transducer (Grass FT07) and connected to a polygraph (Grass Model 7) to measure isometric contractile force as previously described (Pérez-Vizcaíno *et al.*, 1991). The tissue bath was maintained at 37°C and bubbled with 95% O_2-5%CO_2 gas mixture. Each preparation was allowed to equilibrate for 90 min before experimental procedures were started, and during this period the incubation medium was changed every 30 min. The absence of functional endothelium was confirmed by the inability of the preparation precontracted with 10^{-6}M NA to relax in response to 10^{-6}M acetylcholine.

Effects of quinidine and quinine on KCl-induced contractions

After equilibration, aortic rings were exposed to 80 mM KCl. When the tonic contractile response was stable, concentration-response relaxation curves were obtained for quinidine and quinine by cumulative addition of the drugs. The relaxant effect of each concentration was allowed to reach a stable level (normally after 25–35 min) before the next concentration was added and expressed as percentage of relaxation of the contraction induced by KCl. Parallel time controls did not decline more than 5–10% during the period of study. In another set of experiments, after equilibration, a contractile response to 80 mM KCl in rat aortic rings was recorded for 40 min and then washed in normal PSS to reach again the basal tension value. Thereafter, rings were exposed to vehicle, quinidine (6×10^{-6}M, 2×10^{-5}M or 6×10^{-5}M) or quinine (10^{-5}M, 3×10^{-5}M or 10^{-4}M) for 40 min and, finally, rings were again contracted by addition of 80 mM KCl PSS for another 40 min in the presence or in the absence of the drug.

To examine the voltage-dependence of quinidine- and quinine-induced inhibition the following protocol was employed (Pérez-Vizcaíno *et al.*, 1994). The effect of the drugs was studied under different membrane potentials which were controlled by changing the extracellular concentration of KCl ('potassium clamp'; Burgess *et al.*, 1987; Pérez-Vizcaíno *et al.*, 1994). The effect of the drugs was examined by incubating the aortic rings in 5 or 40 mM KCl, Ca^{2+}-free PSS (isotonic replacement of NaCl by KCl). Then a strong depolarizing test pulse inducing a contraction was applied by changing the bath solution to a 100 mM KCl, 2 mM $CaCl_2$ PSS. Three control contractile responses were obtained at the beginning of the experiment at 30 min intervals. This was followed by exposure to quinidine (6×10^{-6}M, 2×10^{-5}M and 6×10^{-5}M) or quinine (3×10^{-6}M, 10^{-5}M, 3×10^{-5}M and 10^{-4}M) for 40 min. The contractile response was then elicited in the presence of the drug. In each ring only one drug and one concentration of KCl were tested. In parallel time controls the responses were in the range of 90 to 108% of the first initial controls. The results of these experiments are expressed as a percentage of the initial control contractile responses.

Effects of quinidine and quinine on concentration-response curves to NA, 5-hydroxytryptamine (5-HT) and endothelin-1 (ET-1)

After equilibration, rings were exposed to 80 mM KCl to test their viability. After washing, rings were exposed to vehicle, quinidine (6×10^{-6}M–2×10^{-4}M) or quinine (10^{-5}M–3×10^{-4}M) for 30 min and then a concentration-response curve was obtained by cumulative increases of NA (10^{-9}M–10^{-4}M), 5-HT (10^{-8}M–3×10^{-5}M) or endothelin-1 (10^{-11}M–10^{-8}M) concentration.

Effects of quinidine and quinine on the responses to 5-HT in Ca^{2+}-free media

After equilibration, rings were exposed to 80 mM KCl to test their viability. After washing, rings were washed three times in Ca^{2+}-free medium containing 0.1 mM EGTA for 30 min. At this time, the addition of 10^{-5}M 5-HT elicited a transient contraction and 10 min later extracellular Ca^{2+} was restored by addition of 2 mM $CaCl_2$ to the bathing media which induced a stable tonic contraction. The same experimental protocol was performed in the presence of quinidine (6×10^{-5}M or 2×10^{-4}M) or quinine (10^{-4}M or 3×10^{-4}M).

Drugs and statistics

The following drugs were used: quinidine sulphate, quinine hydrochloride, (−)-noradrenaline bitartrate, acetylcholine chloride, 5-hydroxytryptamine creatine sulphate complex, endothelin-1, and EGTA (Sigma Ltd. Co., London). All drugs were dissolved in distilled deionized water to prepare a 10^{-2}M or 10^{-3}M stock solution and further dilutions were made in PSS. Ascorbic acid (Merk, 10^{-4}M) was added to the stock solution of NA. Quinidine sulphate contains two moles of quinidine base per mol but the concentrations were expressed as final quinidine base concentrations.

Throughout the paper, values are expressed as mean ± s.e.mean. Statistical analysis was performed by means of an unpaired Student's *t*-test. For multiple comparisons statistically significant differences were analysed by an ANOVA test followed by a Duncan's test. The differences between control and experimental values were considered significant when $P<0.05$. Concentration-response curves in each ring were fitted to a logistic equation. The negative logarithm of the concentration of drug producing 50% of the maximal response (pD_2) was obtained from this fitted equation. The pA_2 values were calculated by Schild-plot analysis (Arunlakshana & Schild, 1959).

Results

Effects of quinidine and quinine on KCl-induced contractions

Addition of KCl (80 mM) to rat aortic rings induced a contractile response which averaged 1682 ± 188 mg (n = 12). As shown in Figure 1, cumulative increases in the concentration of quinidine or quinine (10^{-6}M–3×10^{-4}M) resulted in a concentration-dependent relaxation, the pD_2 values being 4.89 ± 0.05 (n = 6) and 4.23 ± 0.12 (n = 6), respectively. Thus, quinidine was about 4–5 times more potent than quinine ($P<0.01$). Pretreatment of rat aortic rings with quinidine or quinine also resulted in a concentration-dependent inhibition of KCl-induced contractions. The calculated pD_2 values for quinidine and quinine were 4.49 ± 0.05 and 3.91 ± 0.01, respectively ($P<0.01$). Thus, quinidine was about 4 times more potent than quinine under these experimental conditions.

The voltage-dependence of drug-induced inhibitory effects was studied under different membrane potentials which were controlled by changing the extracellular concentration of KCl (5 or 40 mM). As shown in Figure 2a quinidine was more

potent at inhibiting the contractions induced by 100 mM KCl, 2 mM Ca^{2+} when the rings were simultaneously incubated with quinidine and 40 mM KCl (pD_2 = 4.83 ± 0.05), i.e. under depolarizing conditions, when compared to normally polarized rings (5 mM KCl, pD_2 = 4.55 ± 0.04, $P<0.05$). These results indicated that the effects of quinidine were voltage-dependent. In contrast, the inhibitory effects of quinine were similar in aortic rings incubated with 5 or 40 mM KCl (Figure 2b), i.e. they seem to be voltage-independent (the pD_2 values were 4.42 ± 0.07 and 4.40 ± 0.06, respectively).

Effects of quinidine and quinine on the concentration-response curves to NA

The effects of quinidine and quinine on the concentration-response curve to NA are shown in Figure 3. The maximal control responses to NA averaged 1743 ± 114 mg. The antagonism of NA-induced contractions by low concentrations of quinidine (6×10^{-6}M–6×10^{-5}M) and quinine (10^{-5}M–10^{-4}M) was competitive, as demonstrated by the concentration-dependent parallel rightward shift of the NA concentration-response curves with no significant reduction in the maximal response. The inset in Figure 3 shows that for these low concentrations of quinidine and quinine, the slope of the Schild-plot yielded values not significantly different from unity (0.94 ± 0.13 and 1.06 ± 0.22, for quinidine and quinine, respectively). The calculated pA_2 values were 6.20 ± 0.26 and 5.68 ± 0.30, respectively, which indicated that quinidine was about 3–4 times more potent than quinine ($P<0.05$). In contrast, at the highest concentrations tested, both quinidine (2×10^{-4}M) and quinine (3×10^{-4}M) also decreased the maximal response to NA and thus, shifted the concentration-response curve downwards and to the right.

Effects of quinidine and quinine on the concentration-response curves to 5-HT and ET-1

The effects of quinidine and quinine were also studied on the contractions induced by 5-HT (10^{-8}M–3×10^{-5}M) and ET-1 (10^{-11}M–10^{-8}M). The maximal control responses to 5-HT and ET-1 averaged 1808 ± 141 (n = 8) and 1965 ± 143 mg (n = 6), respectively. Low concentrations of quinidine or quinine ($\leqslant 3 \times 10^{-5}$M) had no effect on the concentration-response curve to 5-HT or ET-1 (Figures 4 and 5). At higher concentrations ($\geqslant 10^{-4}$M) both drugs decreased the maximal contractile responses to 5-HT and ET-1 and shifted the concentration-response curves downwards. These inhibitory effects of quinidine and quinine on the contractions induced by 5-HT and ET-1 were not stereoselective.

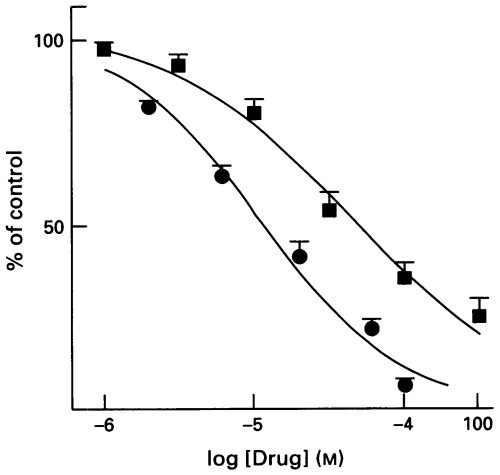

Figure 1 Relaxant effects of quinidine (●) and quinine (■) on rat aortic rings precontracted with KCl (80 mM). After the contraction induced by KCl (80 mM) reached its plateau, concentration-response curves were performed by cumulative addition of the drugs. Each symbol represents the mean ± s.e.mean of 5–6 rings from different animals. Ordinate scale: percentage of the initial control tension. Abscissa scale: log drug concentration (M).

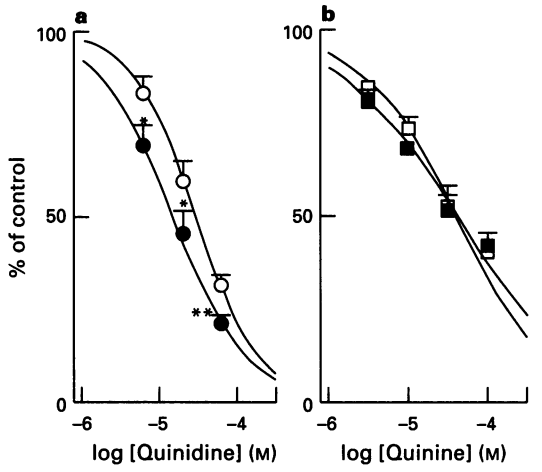

Figure 2 Voltage-dependence of the effects of (a) quinidine and (b) quinine. The rings were incubated in either 5 (○,□) or 40 mM KCl (●, ■) Ca^{2+}-free PSS and then contracted by changing the solution to a 100 mM KCl 2 mM Ca^{2+} PSS for 2 min. Ordinate scale: percentage of control. Abscissa scale: log drug concentration (M). Each symbol represents the mean ± s.e.mean of 5–6 rings from different animals.

Effects of quinidine and quinine on the response to 5-HT in Ca^{2+}-free media

In aortic rings incubated in Ca^{2+}-free media (0.1 mM EGTA) addition of 10^{-5}M 5-HT induced a phasic contraction averaging 302 ± 4 mg (n = 7). After 10 min, the extracellular Ca^{2+} concentration was increased to 2 mM, which resulted in a tonic contraction (1987 ± 190 mg). When added to Ca^{2+}-free media, quinidine (6×10^{-5}M) or quinine (10^{-4}M) had no effect on either the phasic or the tonic contractions (Figure 6). However, at higher concentrations quinidine (2×10^{-4}M) or quinine (3×10^{-4}M) inhibited ($P<0.05$) both the phasic and tonic responses to a similar extent.

Discussion

In the present paper we have analysed and compared the effects of quinidine and its enantiomer quinine on the contractile responses induced by KCl, NA, 5-HT and ET-1 in endothelium-denuded rat isolated aorta. Both quinidine and quinine produced a concentration-dependent inhibition of 80 mM KCl-induced contractions and this inhibitory effect was observed when the drugs were added before or after the induced contractions. The inhibitory effects of quinidine but not of quinine were increased when the drug was incubated under depolarizing conditions (40 mM KCl). Quinidine and quinine produced a concentration-dependent parallel rightward shift of the concentration-response curves to NA, whereas at the highest concentration tested they also depressed the maximal responses to NA. In these experiments quinidine was 3–5 times more potent than quinine, which indicated that the inhibitory effect on KCl- and NA-induced contractions was stereoselective. In contrast, both drugs only at high concentrations reduced the maximal responses to 5-HT or ET-1 to a similar extent which indicated that their inhibitory effects were not stereoselective.

Contractions induced by depolarization with KCl have been shown to depend on Ca^{2+} entry through voltage-dependent Ca^{2+} channels (Bolton, 1979). In previous experiments in this laboratory and others, it has been demonstrated that some class I antiarrhythmic drugs (i.e., propafenone, flecainide, quinidine, mexiletine, imipramine and desipramine) produced

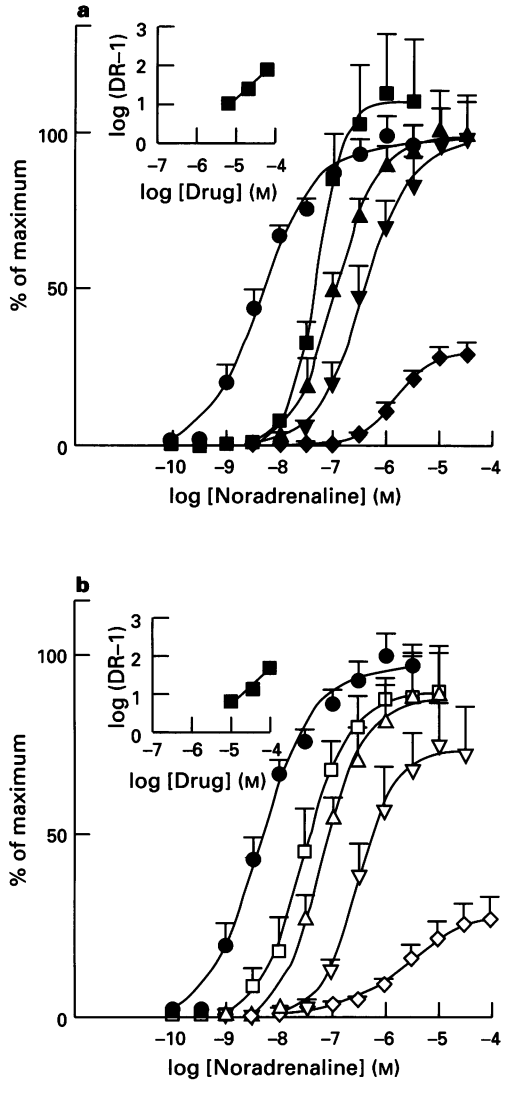

Figure 3 Effects of (a) quinidine and (b) quinine on the concentration-response curves to NA (10^{-10}M–3×10^{-5}M) in rat aortic rings. (a) Control (●); 6×10^{-6}M (■), 2×10^{-5}M (▲), 6×10^{-5}M (▼) or 2×10^{-4}M quinidine (◆). (b) Control (●), 10^{-5}M (□), 3×10^{-5}M (△), 10^{-4}M (▽) and 3×10^{-4}M quinine (◇). Ordinate scale: percentage of maximal response in control; abscissa scale: log noradrenaline concentration (M). Each symbol represents the mean ± s.e.mean of 4–6 rings. Insets: Schild-plot analysis. Ordinate scale: log(dose ratio −1); abscissa scale: log quinidine or quinine concentration (M).

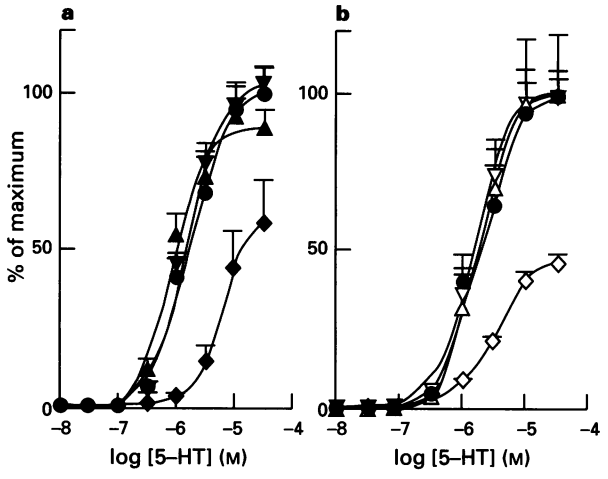

Figure 4 Effects of (a) quinidine and (b) quinine on the concentration-response curves to 5-HT (10^{-8}M–3×10^{-5}M) in rat aortic rings. (a) Control (●); 2×10^{-5}M (▲), 6×10^{-5}M (▼) and 2×10^{-4}M quinidine (◆); (b) Control (●); 3×10^{-5}M (▲), 10^{-4}M (▽), and 3×10^{-4}M quinine (◇). Ordinate scale: percentage of maximal response in control; abscissa scale: log 5-HT concentration (M). Each symbol represents the mean ± s.e.mean of 4–8 rings.

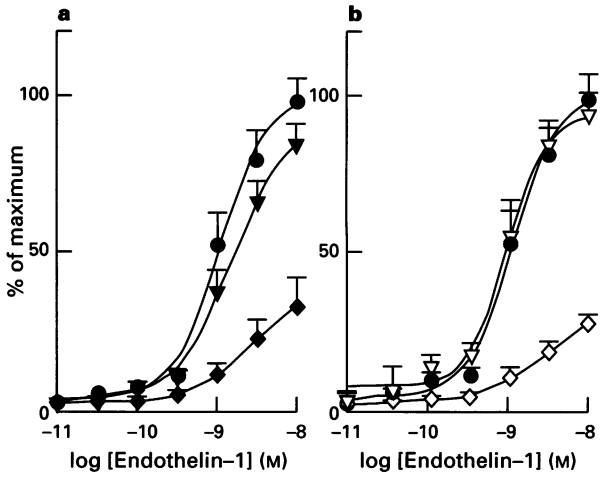

Figure 5 Effects of (a) quinidine and (b) quinine on the concentration-response curves to ET-1 (10^{-11}M–10^{-8}M) in rat aortic rings. (a) Control (●); 6×10^{-5}M (▼) and 2×10^{-4}M quinidine (◆); (b) Control (●); 10^{-4}M (▽) and 3×10^{-4}M quinine (◇). Ordinate scale: percentage of maximal response in control; abscissa scale: log ET-1 concentration (M). Each symbol represents the mean ± s.e.mean of 5–6 rings.

vasorelaxant effects that can be attributed to Ca^{2+} entry blockade (Carrón *et al.*, 1991; Pérez Vizcaíno *et al.*, 1991; 1994; Dohi *et al.*, 1994; Fernández del Pozo *et al.*, 1994). In the present study, quinidine and quinine inhibited in a concentration-dependent manner KCl-induced contractions, an effect that can be related to their ability to inhibit Ca^{2+} entry through L-type Ca^{2+} channels. In fact, quinidine inhibited KCl-induced contractions at the same range of concentrations at which it inhibited KCl-induced $^{45}Ca^{2+}$ entry in rat aorta (Pérez-Vizcaíno *et al.*, 1994) or Ca^{2+} currents in cardiac myocytes (pD_2 = 4.69, Scamps *et al.*, 1989). Furthermore, the pD_2 for quinine to inhibit KCl-induced contractions in this work was similar to that at which the drug inhibited $^{45}Ca^{2+}$ uptake in A7r5 cells, a rat foetal aortic smooth muscle derived cell line (pD_2 = 4.0, Cook & Quast, 1990). Moreover, this inhibition of Ca^{2+} entry seems to be stereoselective, quinidine being more potent than quinine. Stereoselective block of Ca^{2+} channels has been previously reported with different Ca^{2+}-antagonists including dihydropyridines (Towart *et al.*, 1981; Mannhold *et al.*, 1982) and phenylalkylamines (Bayer *et al.*, 1975).

According to the modulated receptor hypothesis (Hondeghem & Katzung, 1984), binding of a drug to its receptor located within the channel is modulated by the conformational state of the channel (rested, activated or inactivated) which is determined by the membrane potential. Some Ca^{2+} channel blockers (e.g. isradipine, nisoldipine or lacidipine) show a greater affinity for vascular L-type Ca^{2+} channels under depolarizing conditions and therefore exert greater inhibitory effects in these situations (Wibo *et al.*, 1988; Salomone & Godfraind, 1993). Since depolarization of the membrane potential shifts the conformation of Ca^{2+} channels into the activated and inactivated states, the voltage-dependence of Ca^{2+} channel blockade has been attributed to a preferential binding to these states of the channel compared to the rested state (Bean *et al.*, 1986; Tamargo & Delpon, 1991). In fact, most Ca^{2+} channel blockers exhibit a higher affinity for the inactivated state than for the activated and rested states (Bean *et al.*, 1986; McDonald *et al.*, 1994). In the present experiments,

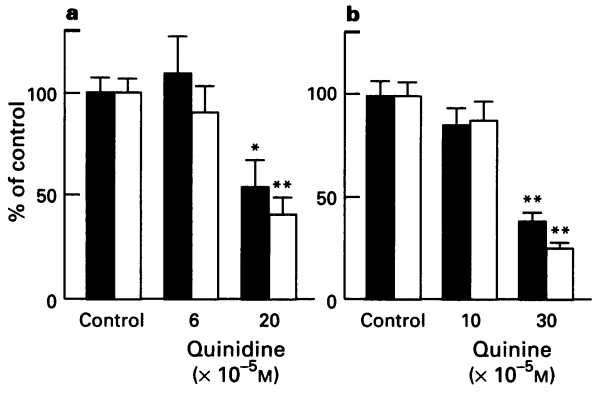

Figure 6 Effects of (a) quinidine and (b) quinine on the phasic contractions induced by 5-HT in Ca^{2+}-free media (solid columns) and on the tonic contractions after restoring the extracellular Ca^{2+} concentration (2 mM, open columns). Preparations were incubated for 30 min in Ca^{2+}-free solution (0.1 mM EGTA) in the absence (control) or presence of the appropriate concentration of the drugs and then stimulated by 5-HT to induce the phasic contraction. After 10 min Ca^{2+} was restored to the bathing media by addition of 2 mM $CaCl_2$ to induce a tonic contraction. Each column is the mean ± s.e.mean of 6–7 experiments expressed as a percentage of control values. $*P<0.05$ and $**P<0.01$ compared to control values.

the effects of quinidine (but not of quinine) were augmented when the aortic rings were exposed to the drugs under depolarizing conditions (in 40 mM KCl PSS). Therefore, the voltage-dependence of the Ca^{2+} channel blocking actions of these drugs also appears to be stereoselective.

The inhibitory effects of quinine and quinidine on adrenoceptor-mediated responses has been known for more than 60 years (Nelson, 1928). In the present study, quinidine or quinine ($\leqslant 10^{-4}$M) produced a concentration-dependent rightward shift of the concentration-response curve for NA. The analysis of the Schild-plot yielded slope values not different from unity indicating a competitive inhibition of α_1-adrenoceptors. In binding studies, quinidine has been reported to be a competitive antagonist of α_1- and α_2-adrenoceptors in rat cardiac membranes, human platelets and rat kidney (Motulsky *et al.*, 1984). Because in the rat aorta, the vasoconstrictor effect of NA appears to be mediated by an activation of α_{1D}-adrenoceptors (Saussy *et al.*, 1994; Kenny *et al.*, 1995), quinidine and quinine behave as competitive antagonists of the α_{1D}-adrenoceptors. This antagonism was stereoselective, quinidine being significantly more potent than quinine.In contrast, at low concentrations quinine and quinidine did not shift the concentration-response curve to 5-HT or ET-1, whereas at high concentrations they produced a non stereoselective depression of the maximal contractile responses. This effect was produced in a very narrow range of concentrations, since at $\leqslant 10^{-4}$M the drugs had no effect but the inhibition was greater than 50% at concentrations between 10^{-4}M and 3×10^{-4}M. High concentrations of quinine (3×10^{-4}M) also inhibited the maximal response to angiotensin II in rabbit aorta in a non-competitive manner (Cook *et al.*, 1987). The inhibitory effects induced by high concentrations of quinidine and quinine on the maximal responses to vasoconstrictor agents acting on different membrane receptors cannot be explained by an interference with the specific receptors but to an interaction with a common process beyond receptor activation. Thus, we investigated the possibility that an action of quinidine and quinine on Ca^{2+}-release from intracellular stores or Ca^{2+}-entry through the plasma membrane following the activation of receptors is present at such high concentrations. Both enantiomers inhibited the phasic contractions elicited by 5-HT in Ca^{2+}-free media (due to the release of Ca^{2+} from intracellular stores) as well as the tonic contraction elicited when the extracellular Ca^{2+} concentration was restored (contractions due to Ca^{2+} entry). The degree of inhibition of both contractions was similar and non stereoselective. Since we did not measure intracellular Ca^{2+} levels it is difficult to speculate if these effects were due to a simultaneous interference with Ca^{2+} release from intracellular stores and Ca^{2+} entry and/or to an interference with a step beyond agonist-mediated increase in intracellular Ca^{2+}.

Systemic administration of quinidine is commonly associated with a decrease in arterial pressure, a side effect that can be clinically important (Mariano *et al.*, 1992). This effect has been attributed to postjunctional peripheral inhibition of α_1-adrenoceptors but also to a non-adrenergic mechanism since denervated extremities also vasodilate following quinidine administration (Schmid *et al.*, 1974; Nelson *et al.*, 1974; Mariano *et al.*, 1992). The present data support that the Ca^{2+}-channel blocking properties of quinidine can account for this non-adrenoceptor mediated vasodilatation. The action of quinine on the cardiovascular system is qualitatively similar to that of quinidine. At therapeutic doses quinine has little effect on the normal heart or blood pressure in man, but given as a bolus intravenously can cause alarming and even fatal hypotension (Bateman & Dyson, 1986). Therefore, from the present results this hypotension can be explained by its α_1-adrenoceptor antagonism together with its Ca^{2+} channel blocking properties. The non specific inhibitory effect of quinidine and quinine on agonist- (non α-adrenoceptor-) mediated contractions would be expected to play a role only following drug overdosage.

In conclusion, quinidine and quinine produce a stereoselective inhibition of depolarization-induced contraction in vascular smooth muscle due to Ca^{2+} channel blockade, quinidine being 4–6 times more potent than its enantiomer quinine. The drugs also behaved as competitive antagonists of NA-induced contractions in rat aorta which are mediated by α_{1D}-adrenoceptors, this effect was also stereoselective, quinidine being about 3–4 times more potent. At high concentrations the drugs also exert a non specific inhibitory effect against the contractions induced by ET-1 and 5-HT.

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