J. Pharm. Pharmacol. 2000, 52: 99–105
Received April 16, 1999
Accepted August 2, 1999

Influence of Extracellular K^+ Concentrations on Quinidine-induced K^+ Current Inhibition in Rat Ventricular Myocytes

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Abstract

Hypokalaemia is one of the important risk factors for development of torsades de pointes. We recently reported that hypokalaemia increased the electrocardiographic QT interval in rats treated with quinidine, but did not alter the arrhythmogenic potency of quinidine. In this study, we have investigated the influence of extracellular potassium concentration ($[K^+]_o$) on the inhibition of several types of cardiac potassium currents by quinidine. Such types of currents include the delayed rectifier potassium current (I_K), the transient outward current (I_{to}), and the inward rectifier potassium current (I_{K1}), as measured in isolated rat ventricular cells using patch-clamp techniques.

Concentration-dependent effects of quinidine on I_K, I_{to}, and I_{K1} were evaluated under both normal ($[K^+]_o = 5{\cdot}4$ mM) and hypokalaemic ($[K^+]_o = 3{\cdot}5$ mM) conditions. In contrast to both I_K and I_{to}, which were barely influenced by changes in $[K^+]_o$, I_{K1} was significantly inhibited by hypokalaemia. Furthermore, while quinidine suppressed both I_K and I_{to} in a concentration-dependent manner, the inhibitory potency of quinidine on these currents was not influenced by changes in $[K^+]_o$. The respective normal and hypokalaemic IC50 values for quinidine were 11·4 and 10·0 μM (I_K), and 17·6 and 17·3 μM (I_{to}). Although higher concentrations of quinidine were required to inhibit I_{K1}, the inhibitory potency of quinidine was also found to be insensitive to changes in $[K^+]_o$. Thus, in rats, the inhibitory potency of quinidine for the K^+ current-types I_K, I_{to} and I_{K1} is barely influenced by changes in $[K^+]_o$.

These findings are consistent with our previous report showing that the QT-prolonging potency of quinidine was not altered under hypokalaemic conditions. However, whilst hypokalaemia does not affect I_K or I_{to}, it can inhibit I_{K1} and can result in QT prolongation in-vivo.

Potassium channels play an important role in the repolarization process of cardiac action potentials, and their blockade results in prolongation of the action potential. Action potential duration for cardiac myocytes is considered to be reflected by the QT interval parameter in electrocardiography, and it has been shown that K^+-channel blockade results in the prolongation of QT interval in-vivo (Roden & George 1997). Furthermore, it has been demonstrated that blockade of the delayed rectifier potassium current (I_K), the transient outward current (I_{to}), and/or the inward rectifier potassium current (I_{K1}) induces QT prolongation both in-vivo and in-vitro (Wallace et al 1991; Rees & Curtis 1993; Rees et al 1993).

The extracellular potassium concentration ($[K^+]_o$) is also known to affect the electrophysiological properties of cardiac myocytes (Podrid 1990). This is of great importance clinically, as it is recognized that hypokalaemia is not merely a risk factor (Kay et al 1983) but also a primary cause of fatal arrhythmias, including torsades de pointes (TdP) (Curry et al 1976; Chvilicek et al 1995). Since the incidence of TdP is heralded

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by QT prolongation on the electrocardiogram, the electrophysiological properties of potassium channels, which directly affect action potential, may in turn be influenced by $[K^+]_o$ in-vitro. Thus, using cultured mouse atrial cardiomyocytes (AT-1 cells), Yang & Roden (1996) showed that decreasing $[K^+]_o$ (from 8 to 4 mM) resulted in a 25% decrease in I_{Kr} (rapid component of the delayed rectifier potassium current), and also potentiated quinidine-induced inhibition of I_{Kr}. However, we have recently reported that, in rats, the arrhythmogenic potency of quinidine, as assessed by QT prolongation, did not change under hypokalaemic conditions, albeit that QT intervals were significantly prolonged by hypokalaemia (Hirota et al 1998). Therefore, in this study, we have evaluated the influence of $[K^+]_o$ on cardiac potassium currents of rat ventricular cells, and the inhibitory potency of quinidine on such potassium currents in-vitro to permit comparison with the electrophysiological findings previously observed in-vivo.

Materials and Methods

Cell preparation

Single ventricular cells were isolated from rat heart by an enzymatic dissociation method (Watanabe et al 1996). Briefly, male rats, 270–370 g, were anaesthetized with pentobarbital sodium and ventilated with an artificial respirator. The heart was removed from the thoracic cavity and mounted on a modified Langendorff perfusion system, designed to permit retrograde perfusion of the coronary circulation with standard HEPES–Tyrode solution. Subsequently, the perfusion medium was changed to a nominally Ca^{2+}-free Tyrode solution for 5 min, and then exchanged for a solution containing 0·03% w/v collagenase for 25–32 min. After digestion, the heart was perfused with a high K^+/low Cl^- solution; a modification of the Kraftbrühe solution (Isenberg & Klockner 1982). The ventricular tissue was then cut into small pieces in the modified Kraftbrühe solution and gently shaken to isolate the cells. The cell suspension was filtered through a 100-μm-pore stainless steel mesh and stored at 4°C for future use.

Solutions

The composition of standard HEPES–Tyrode solution was (in mM): NaCl, 143; KCl, 5·4; $CaCl_2$, 1·8; $MgCl_2$, 0·5; NaH_2PO_4, 0·33; glucose, 5·5; and HEPES–NaOH buffer, 5·0 (pH 7·4). Nominally Ca^{2+}-free Tyrode solution was prepared by omitting $CaCl_2$ from standard Tyrode solution. The composition of the modified Kraftbrühe solution was (in mM): KOH, 70; L-glutamic acid, 50; KCl, 40; taurine, 20; KH_2PO_4, 20; $MgCl_2$, 3; glucose, 10; EGTA, 1·0; and HEPES–KOH buffer, 10 (pH 7·4). In some experiments, the KCl concentration in the HEPES–Tyrode solution was reduced to 3·5 mM. Quinidine (0·6–200 μM) solutions were made up in the HEPES–Tyrode solution, additionally containing 3·0 mM Co^{2+} in order to block the L-type Ca^{2+} current. In some experiments, the 80 mM NaCl in the Tyrode solution was replaced with 80 mM tetraethylammonium chloride (TEA), or 3·0 mM 4-aminopyridine (4AP) in order to block I_K and I_{to}, respectively. The pipette solution was composed of (in mM): KOH, 110; L-aspartate, 110; KCl, 20; $MgCl_2$, 1·0; potassium ATP, 5·0; potassium phosphocreatine, 5·0; EGTA, 10; and HEPES–KOH buffer, 5·0 (pH 7·4). The free Ca^{2+} concentration in the pipette solution was adjusted to pCa 8 according to the algorithm of Fabiato & Fabiato (1979), with the correction of Tsien & Rink (1980).

Electrophysiological recordings

Whole cell membrane currents were recorded by a patch-clamp method (Hamill et al 1981). Single ventricular myocytes were placed in a recording chamber (1·0-mL volume), attached to an inverted microscope (Model IMT-2, Olympus, Tokyo, Japan) and superfused with the HEPES–Tyrode solution at a rate of 3 mL min^{-1}. The temperature of the bath solution was maintained at 36.0 ± 1·0°C. Patch pipettes were made from glass capillaries (1·5 mm o.d., Narishige, Tokyo, Japan), using a vertical microelectrode puller (Model PB-7, Narishige). Pipettes, with a tip diameter of 2–3 μm, were then heat-polished and filled with an internal solution described above. The tip resistance was measured as 2–3 MΩ. After formation of the gigaohm seal between the tip and the cell membrane, an increased negative pressure was applied to disrupt the membrane patch and make the whole cell voltage-clamp mode.

The electrode was connected to a patch-clamp amplifier (Model CEZ-2300, Nihon Kohden, Tokyo, Japan). Recording signals were filtered at 1 kHz bandwidth, and series resistance was compensated. Command pulse signals were generated using a 12-bit digital-to-analog converter, controlled by PCLAMP software (Axon Instruments, Foster City, CA). Current signals were digitized with a sampling interval of 2 kHz and stored on the hard disk of an IBM-compatible computer (Com-

paq Prolinea 4/50 with a 200 Mbyte hard disk, Houston, TX).

Depolarization-activated outward K^+ currents, i.e. I_K and I_{to}, were measured according to the method of Apkon & Nerbonne (1991). A 100-ms test pulse up to +40 mV was delivered at 0·1 Hz, from a holding potential of −90 mV. To inactivate the Na^+ current the holding potential was preceded by a 15-ms depolarization pulse to −20 mV. I_K was recorded in the presence of 3 mM Co^{2+} and 3 mM 4AP (in order to block I_{Ca} and I_{to}), whereas I_{to} was measured in the presence of 3 mM Co^{2+} and 80 mM TEA (in order to block I_{Ca} and I_K). Subsequently, the dose–response effect of quinidine on I_K was evaluated by measuring the difference between the current remaining at the end of the 100-ms test pulse in the presence of quinidine compared with that in the presence of TEA. Total I_{to} was calculated as the integral of the outward currents, measured at initiation of the 100-ms test pulse, with respect to the ''steady-state'' currents remaining at the end of the pulse (Slawsky & Castle 1994). The effect of quinidine on I_{to} was evaluated by measuring the difference between total I_{to} in the presence of quinidine compared with that in the presence of 4AP. The magnitude of outward currents, when measured in individual cells exposed to various concentrations of quinidine, was normalized with respect to the current measured in the absence of quinidine. I_{K1} was measured in the presence of 3 mM Co^{2+}, during 300-ms test pulses that ranged between −100 and 0 mV, from a holding potential of −60 mV. I_{K1} was measured as the amplitude of the steady-state currents at the end of the 300-ms test pulse, delivered at 0·1 Hz. Three concentrations (0·6, 6, 60 μM or 2, 20, 200 μM) of quinidine were selected, and the concentration-dependent effects of quinidine were evaluated 3–4 min after drug application.

In order to estimate the effects of $[K^+]_o$ on potassium currents, I_K or I_{to} was measured at 5·4 mM $[K^+]_o$. Thereafter, TEA or 4AP was thoroughly removed by washing, to allow restoration of the currents, and I_K or I_{to} was measured at 3·5 mM $[K^+]_o$. I_{K1} was similarly measured at 5·4 mM $[K^+]_o$ and then at 3·5 mM $[K^+]_o$.

Drugs

Quinidine sulphate dihydrate, 4AP, and collagenase were obtained from Wako Pure Chemical Industries, Ltd (Osaka, Japan). TEA was purchased from Tokyo Kasei Kogyo Co., Ltd (Tokyo, Japan). All other chemicals used were of reagent grade. All drugs were dissolved in distilled water.

Statistics and model analysis

All experimental values are expressed as mean ± s.e.m. Student's *t*-test was employed for statistical analysis of the data. *P* values of less than 0·05 were considered significant. The drug concentrations producing 50% inhibition of potassium currents (IC50) were estimated by fitting the concentration–response curves to an E_{max} model (equation 1), using a non-linear least squares program MULTI (Yamaoka et al 1981), with a modified Marquardt method:

$$E = (1 - C/(IC50 + C)) \times 100\ (\%) \qquad (1)$$

where C represents the concentration of quinidine in the Tyrode solution.

Results

Effects of $[K^+]_o$ on potassium currents

Typical current traces for I_K and I_{to} under normal ($[K^+]_o = 5{\cdot}4$ mM) and hypokalaemic ($[K^+]_o = 3{\cdot}5$ mM) conditions are shown in Figure 1. The amplitudes of I_K and I_{to} under hypokalaemic conditions were 100·4 ± 15·2% and 100·4 ± 8·1% (mean ± s.e.m, n = 5), respectively, of those under normokalaemic conditions, and hence the amplitudes of I_K and I_{to} were not affected by $[K^+]_o$. In contrast, hypokalaemia caused a decrease in I_{K1} (Figure 2A, B), with both outward and inward components of I_{K1} albeit that the decrease in the outward current was less prominent (Figure 2C).

Inhibition of potassium currents by quinidine

Quinidine inhibited I_K in a concentration-dependent manner under both normokalaemic and hypokalaemic conditions (Figure 3). The respective IC50 values of quinidine at 5·4 and 3·5 mM $[K^+]_o$ for I_K were 11·4 and 10·0 μM. Thus, the inhibitory potency of quinidine on I_K was not affected by $[K^+]_o$.

Quinidine also exhibited a concentration-dependent inhibition of I_{to} (Figure 4), and, as before, the inhibitory effect of quinidine on I_{to} was not affected by $[K^+]_o$. The respective IC50 values of quinidine at 5·4 and 3·5 mM $[K^+]_o$ for I_{to} were 17·6 and 17·3 μM.

In contrast, I_{K1} was readily affected by changes of $[K^+]_o$. However, a higher concentration (200 μM) of quinidine was required to cause half-maximal inhibition of I_{K1}. At −50 mV, quinidine (200 μM) suppressed I_{K1} to 56·1 ± 7·4% and 56·6 ± 5·7% of control under normokalaemic and hypokalaemic conditions, respectively. Quinidine

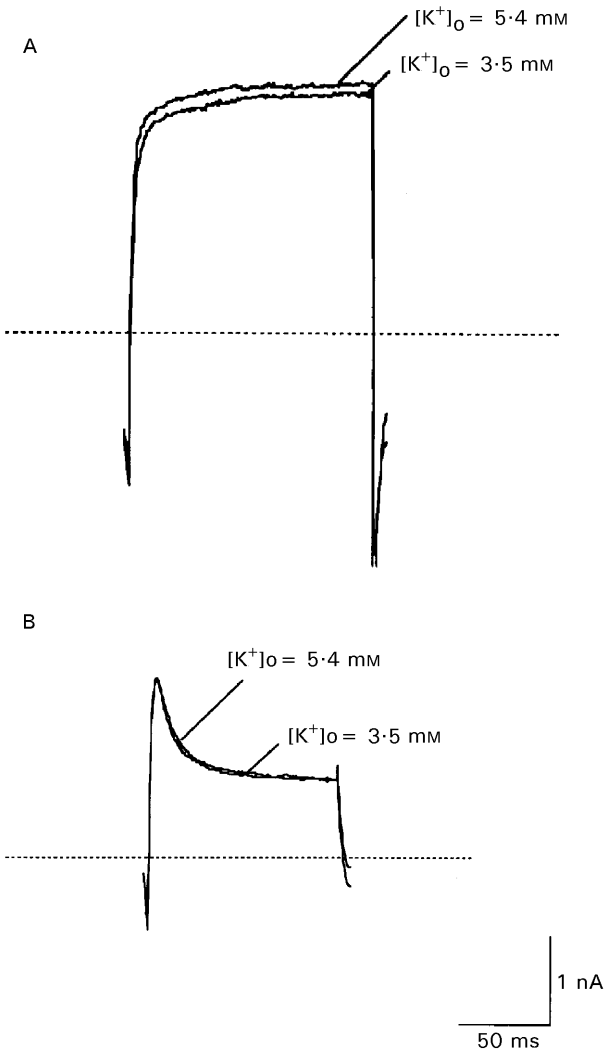

Figure 1. Effects of extracellular potassium on I_K (A) and I_{to} (B). Current traces produced by 100-ms depolarizing pulses from −90 to +40 mV under normokalaemic or hypokalaemic conditions. The horizontal broken line indicates the zero current level.

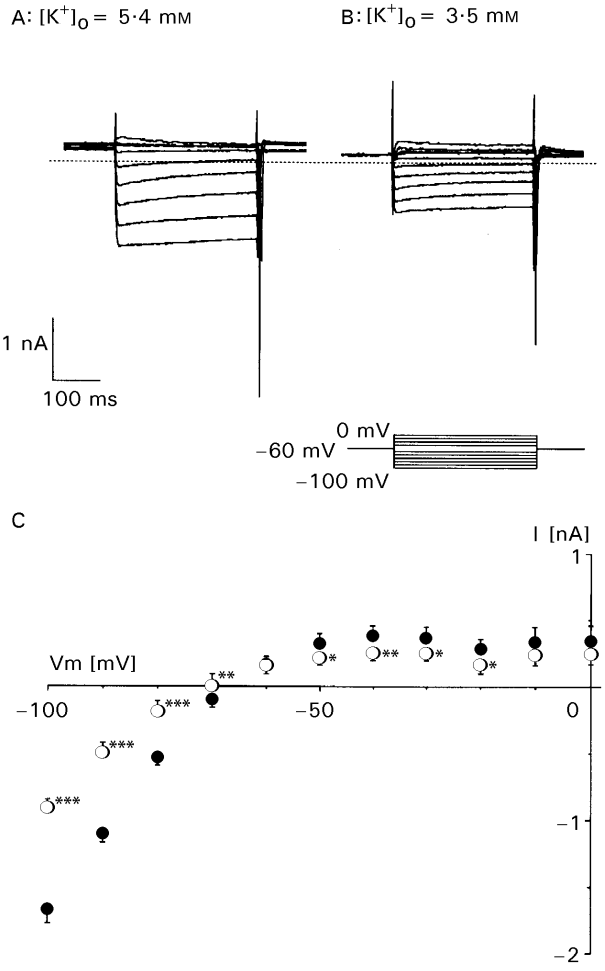

Figure 2. Effects of extracellular potassium on I_{K1}. Families of current traces are depicted that were elicited by a series of 300-ms depolarizing or hyperpolarizing voltage steps (from 0 to −100 mV), from a holding potential of −60 mV at $[K^+]_o$ = 5·4 mM (A) or a $[K^+]_o$ = 3·5 mM (B). The horizontal broken line indicates the zero current level. C. Current–voltage relationship of I_{K1} under normokalaemic and hypokalaemic conditions. $[K^+]_o$ = 5·4 mM ●, $[K^+]_o$ = 3·5 mM ○. Data represents mean ± s.e.m. (n = 5). * $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$.

did not affect I_{K1} at concentrations where half-maximal inhibition of I_K or I_{to} was achieved. The inhibitory potency of quinidine on I_{K1} was not affected by $[K^+]_o$, within the range of −100 to 0 mV (data not shown).

Discussion

In this study, I_K and I_{to} of rat ventricular cells were barely affected by changing $[K^+]_o$, a result at variance with that reported by Yang & Roden (1996). They showed, using AT-1 cells which express I_{Kr} (rapid component of delayed rectifier potassium current) without other overlapping currents, that a decrease in $[K^+]_o$ resulted in a reduction in the amplitude of I_{Kr}. This apparent discrepancy may partially stem from differences in the cell-types used. Thus the I_K observed in rat ventricular myocytes appears to be different from the I_{Kr} expressed in mouse AT-1 cells. In fact, I_K in rat ventricular myocytes is activated much faster than I_{Kr} in guinea-pig heart, indicating that these cells have different electrophysiological properties (Sanguinetti & Jurkiewicz 1990; Apkon & Nerbonne 1991). Thus it would appear that the I_K value in rats is unique when compared with that of other species. The principle component in rats is similar to I_{Kur} (ultra-rapid component of delayed rectifier potassium current), whereas I_{Kr} and I_{Ks} are the principle components in other species, including the human ventricle.

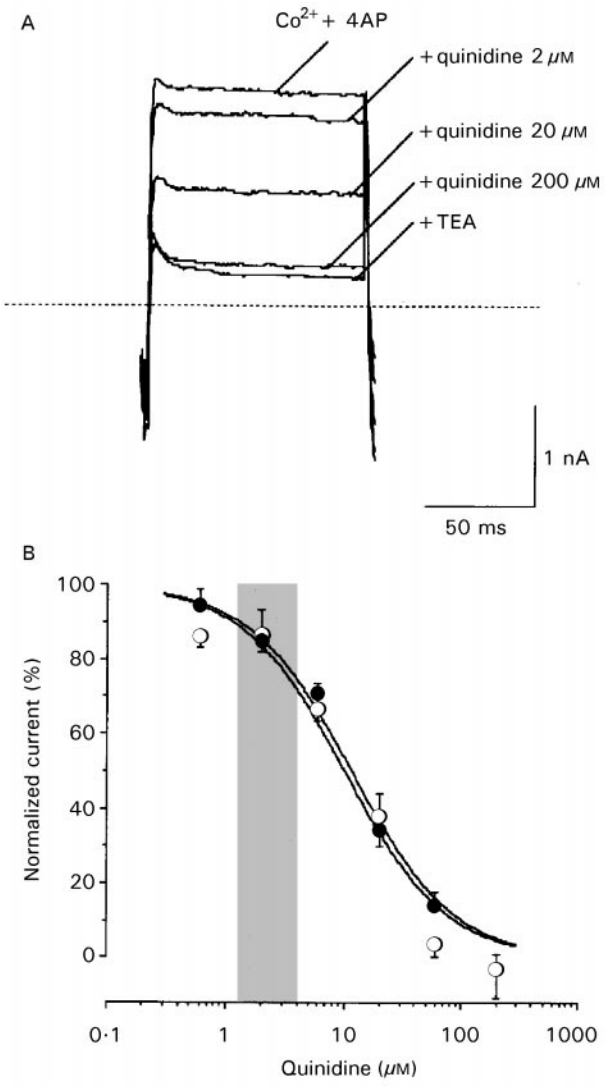

Figure 3. Inhibition of I_K by quinidine. A. A family of current traces is depicted that were produced by 100-ms depolarizing pulses from −90 to +40 mV in the absence or presence of quinidine or TEA. 4AP (3·0 mM) was present in all cases. The horizontal broken line indicates the zero current level. B. Dose–response curves for inhibition of I_K by quinidine. Shaded area represents the therapeutic range for quinidine (free fraction). IC50 values for quinidine at 5·4 and 3·5 mM $[K^+]_o$ were 11·4 and 10·0 μM, respectively. $[K^+]_o = 5·4$ mM ●, $[K^+]_o = 3·5$ mM ○. Data represents mean ± s.e.m. (n = 3–5).

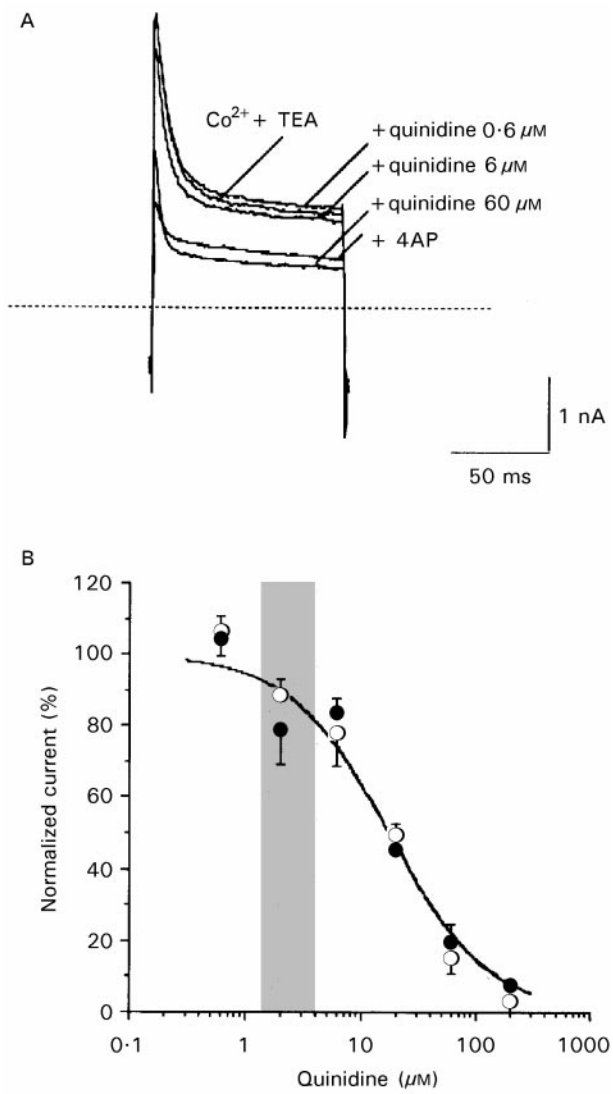

Figure 4. Inhibition of I_{to} by quinidine. A. A family of current traces is depicted that were produced by 100-ms depolarizing pulses from −90 to +40 mV in the absence or presence of quinidine or 4AP. TEA (80 mM) was present in all cases. The horizontal broken line indicates the zero current level. B. Dose–response curves for inhibition of I_{to} by quinidine. Shaded area represents the therapeutic range for quinidine (free fraction). IC50 values for quinidine at 5·4 and 3·5 mM $[K^+]_o$ were 17·6 and 17·3 μM, respectively. $[K^+]_o = 5·4$ mM ●, $[K^+]_o = 3·5$ mM ○. Data represents mean ± s.e.m. (n = 5).

In contrast to I_K and I_{to}, I_{K1} was decreased in response to a reduction in $[K^+]_o$. This finding is consistent with a previous report (Sakmann & Trube 1984) showing that the conductance of I_{K1} was smaller under hypokalaemic conditions in guinea-pig ventricular myocytes. A reduction in I_{K1} resulting from a decrease in $[K^+]_o$ may lead to a prolongation of action potential duration, which could account for the observed increase in QT intervals in hypokalaemic rats, as compared with normal rats observed in our previous study (Hirota et al 1998).

This study shows that the inhibitory potency of quinidine on I_K, I_{to}, and I_{K1} was not influenced by $[K^+]_o$. This is consistent with our previous finding in-vivo, where the QT-prolonging effect of quinidine was not potentiated by hypokalaemia (Hirota et al 1998). However, these findings differ from the study using AT-1 cells (Yang & Roden 1996), where blockade of I_{Kr} by quinidine was potentiated

by decreasing $[K^+]_o$. Such discrepancies may be ascribed to interspecies differences in the characteristics of potassium currents, when comparing between rat ventricular myocytes and mouse AT-1 cells.

In this study, typical concentration-dependent inhibitions of I_K and I_{to} by quinidine were observed in rat ventricular myocytes. From a quantitative perspective, these results are in good agreement with Slawsky & Castle (1994). The therapeutic range for plasma quinidine concentration was reported to be $3-7\,\mu g\,mL^{-1}$ and, with correction for the protein-binding fraction of quinidine (0·8–0·85), this yields a therapeutic plasma unbound concentration of $0{\cdot}45-1{\cdot}4\,\mu g\,mL^{-1}$ ($1{\cdot}4-4{\cdot}3\,\mu M$). In this study, a 10–30% inhibition of I_K and I_{to} was observed within the above range, based on the assumption that the inhibition of these currents was purely attributable to the plasma unbound fraction. Since, in our previous study (Hirota et al 1998), a significant QT prolongation of 15–30 ms was observed within this unbound concentration range, inhibition of I_K and/or I_{to} might be responsible for the quinidine-induced QT prolongation observed in-vivo.

Reports of quinidine inhibition of I_{K1} are conflicting. Several reports using whole cell or single channel recording techniques have shown that quinidine inhibits I_{K1} at concentrations of up to $10\,\mu M$ (Salata & Wasserstrom 1988; Balser et al 1991). In contrast, other studies failed to show any inhibition of I_{K1} by quinidine (Colatsky 1982; Hiraoka et al 1986; Imaizumi & Giles 1987; Slawsky & Castle 1994). In this study, using rat ventricular myocytes, no appreciable blockade of I_{K1} was observed with $10-20\,\mu M$ quinidine, albeit that I_{K1} was half-maximally blocked at $200\,\mu M$ quinidine. Therefore, within the therapeutic range, quinidine-induced QT prolongation is almost certainly not attributable to the blockade of I_{K1}, even when taking into consideration the in-vivo vs in-vitro difference in effective concentration range.

The inhibitory potency of quinidine on I_K or I_{to} was not potentiated by $[K^+]_o$, a result consistent with the previous in-vivo study (Hirota et al 1998). However, some interspecies differences in the electrophysiological properties of the potassium currents may exist, especially when considering I_K (Tseng 1995). Thus, I_K in human ventricles differs from that in rat ventricular cells, which exhibit very rapid activation, but instead may show some similarities to the I_{Kr} of mouse AT-1 cells. Since this study on the effects of hypokalaemia was conducted in rats, a possible potentiation of quinidine-induced inhibition of potassium currents cannot be excluded in man. However, it can be concluded that the overall hypokalaemia-induced decrease of I_{K1} is at least additive to the QT-prolonging effect of quinidine.

In summary, since hypokalaemia may increase the arrhythmogenic risk of administrated drugs, either additively or synergistically, normalization of plasma potassium concentration is a necessary requirement when QT interval-prolonging drugs such as quinidine are administered. Several drugs, frequently used clinically such as steroids and bronchodilators, are renowned in their capacity to decrease plasma potassium concentrations (Isaac & Holland 1992; Howes 1995), and thus should be used with caution when QT-prolonging agents are concomitantly administered.

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