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Low-affinity block of cardiac K^+ currents by nifedipine

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Abstract

Nifedipine inhibits a variety of K^+ currents with IC_{50} between 4 and 40 μM. Among the more sensitive of these are two types (transient outward and ultrarapid hKv1.5) found in the heart. To evaluate the actions of the drug on other prominent cardiac K^+ currents, guinea-pig ventricular myocytes were voltage-clamped for measurement of inwardly rectifying K^+ current (I_{K1}), rapidly activating delayed-rectifier K^+ current (I_{Kr}), and slowly activating delayed-rectifier K^+ current (I_{Ks}). The currents were unaffected by ≤ 10 μM nifedipine, but inhibited by higher concentrations; IC_{50} values were 260 μM for I_{K1}, 275 μM for I_{Kr}, and 360 μM for I_{Ks}. The time- and voltage-dependent properties of I_{Ks} were unaffected by the drug, and full block was attained on the first depolarisation after a rest. The results establish that the sensitivity of I_{Kr} and I_{Ks} to inhibition by nifedipine is approximately 50 times lower than the sensitivity of other cardiac delayed-rectifier K^+ currents.

Keywords: Nifedipine; Ventricular myocyte, guinea-pig; K^+ current, inward-rectifier; K^+ current, delayed-rectifier

1. Introduction

It is well established that nifedipine, the prototype 1,4-dihydropyridine blocker of L-type Ca^{2+} channels (Fleckenstein, 1983; Triggle and Swamy, 1983), blocks delayed-rectifier K^+ channels in a wide variety of non-cardiac cells (Nishi et al., 1983; Terada et al., 1987; Jacobs and DeCoursey, 1990; Pappone and Ortiz-Miranda, 1993; Tatsuta et al., 1994). However, the sensitivity of the channels to inhibition by the drug appears to be quite variable, with reported IC_{50} values ranging from ca. 4 μM (Nishi et al., 1983) to 40 μM (Lin et al., 1995).

At least two types of cardiac delayed-rectifier K^+ currents are amongst those found to be most sensitive to nifedipine. The first of these is the fast-activating inactivating K^+ current (transient outward current (I_{to})) responsible for the early repolarisation phase of the cardiac action potential. Gotoh et al. (1991) reported that I_{to} in rabbit atrial myocytes was inhibited by micromolar concentrations of the drug, and Jahnel et al. (1994) had similar results on I_{to} in rat ventricular myocytes. The second type of cardiac K^+ current sensitive to nifedipine is the ultrarapid-type current (I_{Kur}) carried by hKv1.5 channels cloned from human atrial tissue. Zhang et al. (1997) found that the IC_{50} for interaction of nifedipine with these channels was approximately 6 μM.

To our knowledge, there is no information on the sensitivity of other prominent cardiac K^+ currents to inhibition by nifedipine. These currents include (a) the rapidly activating (I_{Kr}) and slowly activating (I_{Ks}) components of classical delayed-rectifier K^+ current (I_K) (each of which is important for termination of the action potential plateau (Sanguinetti and Jurkiewicz, 1990)), and (b) the inwardly rectifying K^+ current (I_{K1}) responsible for setting the resting potential and driving phase 3 repolarisation. The objective of the present study on guinea-pig ventricular myocytes was to evaluate the sensitivity of I_{Kr}, I_{Ks} and I_{K1} to inhibition by nifedipine.

2. Materials and methods

All procedures were carried out in accordance with national and university regulations on the care and treatment of laboratory animals.

2.1. Ventricular myocytes

Male guinea-pigs (250–300 g) were killed by cervical dislocation, and single ventricular myocytes were enzymat-

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ically isolated as described previously (Ogura et al., 1995). The excised hearts were mounted on a Langendorff column, and retrogradely perfused through the aorta with Ca^{2+}-free Tyrode's solution (37°C) containing collagenase (0.08–0.12 mg/ml: Yakult Pharmaceutical, Tokyo, Japan) for 10–15 min. The cells were dispersed and stored at 22°C in storage solution that contained (in mM) KOH 80, KCl 30, KH_2PO_4 30, $MgSO_4$ 3, glutamic acid 50, taurine 20, ethylene glycol-bis(*b*-aminoethyl ether)-*N*,*N*,*N*,*N*-tetraacetic acid (EGTA) 0.5 and *N*-2-hydroxyethylpiperazine-*N*′-2-ethanesulfonic acid (Hepes) 10 (pH 7.4 with KOH).

A few drops of the cell suspension were placed in a 0.3-ml perfusion chamber mounted on an inverted microscope stage. After the cells had settled to the bottom, the chamber was perfused (2 ml/min) with Tyrode's solution at 36°C. The Tyrode's solution contained (in mM) NaCl 140, KCl 5.4, $CaCl_2$ 1.8, $MgCl_2$ 1, glucose 10, and Hepes 5 (pH 7.4 with NaOH). In some experiments, the Tyrode's solution was replaced by Ca^{2+}-free Tyrode's ($CaCl_2$ omitted) or by K^+-, Ca^{2+}-free Tyrode's solution (KCl and $CaCl_2$ omitted) that also contained 0.2 mM Cd^{2+}.

Whole-cell membrane currents were recorded using an EPC-7 amplifier (List Electronic, Darmstadt, Germany). Recording pipettes were fabricated from thick-walled borosilicate glass capillaries (H15/10/137, Jencons Scientific, Bedfordshire, UK) and filled with solution that contained (in mM) KCl 40, potassium aspartate 106, $MgCl_2$ 1, K_2-ATP 4, (EGTA) 5, and Hepes 5 (pH 7.2 with KOH). The pipettes had resistances of 1.5–2.5 MΩ when filled with pipette solution, and liquid junction potentials between external and pipette-filling solution were nulled prior to patch formation. Series resistance ranged between 3 and 7 MΩ and was compensated by 60–80%. Membrane current signals were filtered at 3 kHz, and digitized with an A/D converter (Digidata 1200A, Axon Instruments) and pCLAMP software (Axon Instruments) at a sampling rate of 8 kHz prior to analysis.

2.2. Drugs

Nifedipine was supplied by Calbiochem (LaJolla, CA, USA) and dissolved in dimethyl sulphoxide (DMSO) (Sigma, St. Louis, MO, USA) as a 0.1-M stock solution.

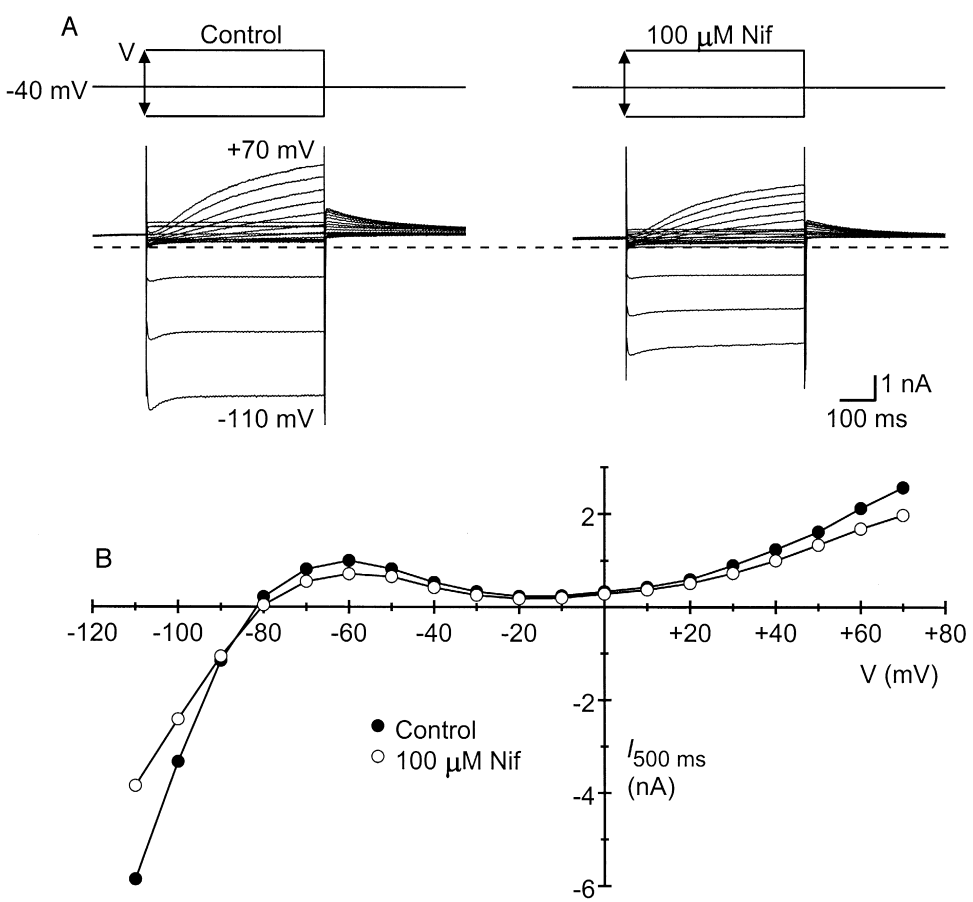

Fig. 1. Effects of nifedipine on K^+ currents in a guinea-pig ventricular myocyte. The myocyte was bathed in Ca^{2+}-free Tyrode's solution, held at −80 mV, and pulsed from prepulse −40 mV to more negative and positive potentials *V* for 500 ms at 0.1 Hz; tail currents were recorded on repolarisations to −40 mV. (A) Records obtained before and 8 min after addition of 100 μM nifedipine. The dashed line in this and other figures indicates the zero-current level. (B) Plot of the *I–V* relationships from this experiment. Current amplitudes were measured at the end of the 500-ms depolarisations and hyperpolarisations by reference to zero current.

The stock solution was stored in the dark at 4°C, and drug solutions were protected from the light during all experiments. The highest final concentration of DMSO in the superfusate was 0.3%, a concentration that has no significant effect on membrane currents in guinea-pig ventricular cells (Ogura et al., 1995). Nevertheless, the appropriate concentrations of DMSO were included in the control solutions used in experiments with high concentrations (30–300 μM) of nifedipine. E4031 (Eisai, Tokyo, Japan) was directly dissolved in bathing solutions.

2.3. Statistics

Results are expressed as means ± SEM, and single comparisons were made using Student's *t*-test. Differences were considered significant when $p < 0.05$.

3. Results

3.1. Inhibition of I_{K1}

Fig. 1A shows records of membrane currents obtained before and after exposure of a myocyte to 100 μM nifedipine. The myocyte was bathed in Ca^{2+}-free solution to eliminate L-type Ca^{2+}-current ($I_{Ca,L}$), held at −80 mV, and pulsed with 500-ms hyperpolarising and depolarising steps from prepulse −40 mV at 0.1 Hz. Current–voltage (I–V) relationships were determined by measuring current amplitudes at the end of the 500-ms steps. The shape of the relationship at voltages negative to −10 mV was typical of that for inward-rectifying I_{K1}, and the drug reduced the amplitude of both inward- and outward-directed I_{K1} by ca. 30% (Fig. 1B). In five experiments with 100 μM nifedipine, inward I_{K1} measured at −110 mV was significantly reduced by 27 ± 4%.

The concentration-dependent effects of nifedipine on outward-directed I_{K1} were evaluated from measurements of the outward current amplitude at −40 mV. Based on the effects of external Ba^{2+} (reduction of the current to near-zero) and 3 μM E4031 (no effect), we have previously shown that this measurement is a valid indicator of the magnitude of outward-directed I_{K1} (Jones et al., 1999). As indicated by the time plots of current amplitudes from representative experiments (Fig. 2A,B), outward I_{K1} was unaffected by low concentrations of nifedipine, and depressed by high concentrations. Inhibition developed rela-

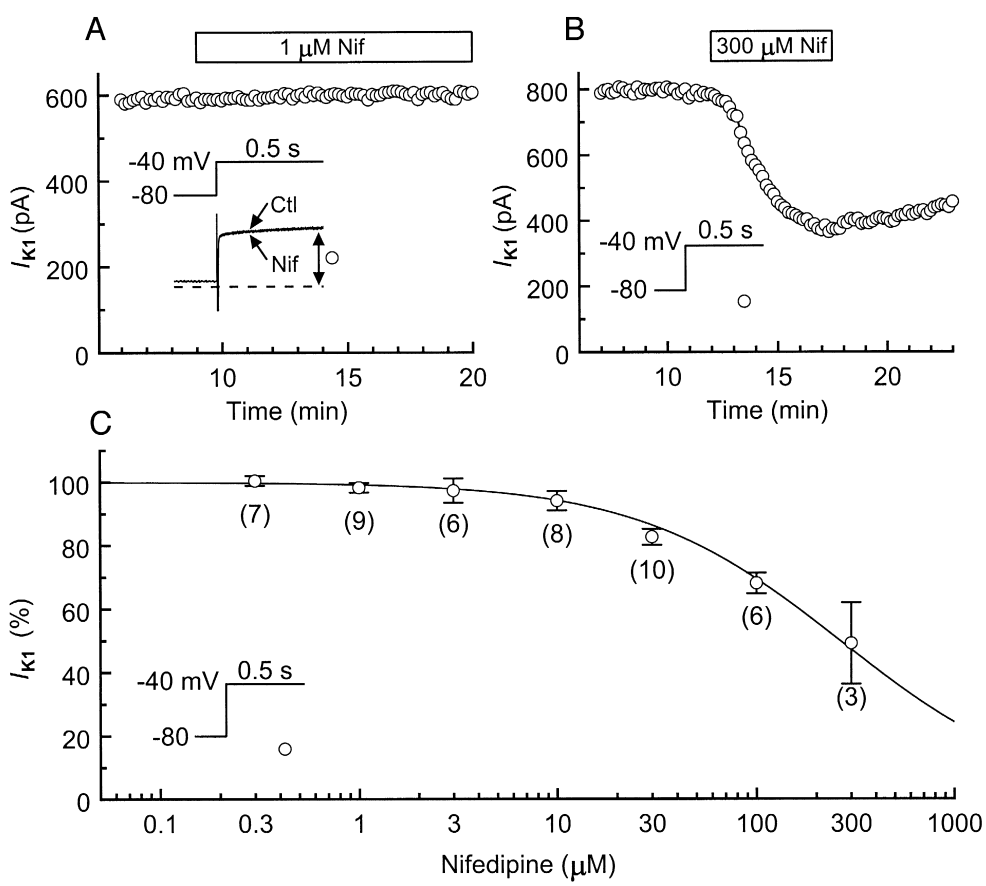

Fig. 2. Inhibition of I_{K1} by nifedipine. (A,B) Data from representative experiments in which outward I_{K1} was measured as the late current amplitude on 500-ms depolarisations from −80 to −40 mV. (C) Dependence of I_{K1} inhibition on the concentration of nifedipine. Myocytes were generally bathed with normal Tyrode's solution, and treated for 7–12 min with one or two concentrations of the drug. The Hill equation fitting the data has an IC_{50} of 260 μM and a coefficient of 0.85. The numbers of myocytes are shown in parentheses.

tively slowly and was difficult to reverse on removal of the drug (Fig. 2B). The data on steady-state inhibition are summarised in Fig. 2C and well-described by the Hill equation with IC_{50} of 260 μM and coefficient of 0.85.

3.2. Inhibition of I_{Kr}

The records in Fig. 1A show that 100 μM nifedipine decreased the amplitude of the time-dependent delayed-rectifier K^+ currents activated during 500-ms depolarisations to voltages V, and decreased the amplitude of the corresponding tail currents (tail I_K) on the repolarisations to −40 mV. Tail I_K amplitudes were measured before and after exposures to nifedipine, and the representative data in Fig. 3A,B illustrate that the tail I_K–V relationship was unaffected by low concentrations of nifedipine, and depressed in a reversible manner by high concentrations. The pattern of inhibition observed with 100 μM nifedipine (Fig. 3B) was different than that observed with I_{Kr}-inhibitor E4031 (i.e., selective inhibition of the low-voltage region of tail I_K–V: Fig. 3C), suggesting that nifedipine was not selective for I_{Kr} over I_{Ks}.

Based on the pattern of inhibition exerted by 3 μM E4031 (Fig. 3C), the amplitude of I_{Kr} was estimated as the amplitude of tail I_K at −40 mV after 500-ms depolarisations to 0 mV. The data are displayed in Fig. 3D, and the Hill equation describing them has an IC_{50} of 275 μM and a coefficient of 0.90.

3.3. Inhibition of I_{Ks}

The effects of nifedipine on slowly activating I_{Ks} were evaluated in myocytes that were depolarised with relatively long (2 s) pulses from −40 mV to more positive potentials. The myocytes were superfused with K^+-, Ca^{2+}-free Cd^{2+} solution to (i) eliminate Ca^{2+}-dependent currents, and (ii) minimise the activation of (external-K^+-

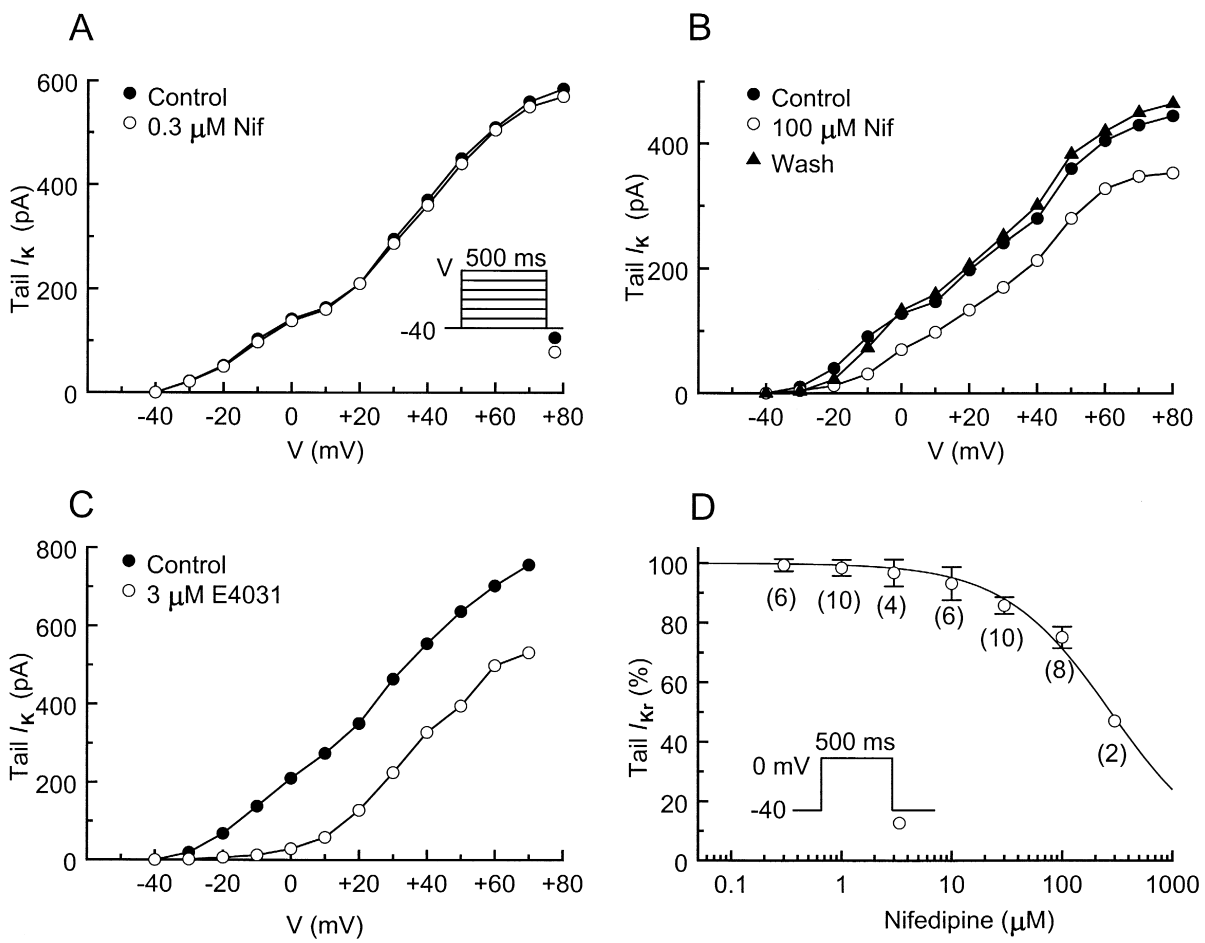

Fig. 3. Inhibition of the I_{Kr} component of tail I_K by nifedipine. Myocytes bathed in normal Tyrode's solution were repolarised to −40 mV for measurement of tail I_K amplitude after 500-ms depolarisations to more positive potentials V. (A,B) Tail I_K–V relationships from representative experiments with nifedipine. Drug exposures lasted for ca. 8 min, and the wash in B lasted for 10 min. (C) Effect of the specific I_{Kr} inhibitor E4031 on the tail I_K–V relationship. (D) Dependence of I_{Kr} inhibition on the concentration of nifedipine. I_{Kr} was evaluated using the amplitude of the tail I_K after 500-ms depolarisations to 0 mV. Myocytes were treated with one or two concentrations of nifedipine for 7 to 10 min each. The Hill equation fitting the data has an IC_{50} of 275 μM and a coefficient of 0.90. The numbers of myocytes are shown in parentheses.

dependent) I_{Kr} and enhance the activation of I_{Ks} (Sanguinetti and Jurkiewicz, 1990; Jones et al., 1998). The records in Fig. 4A,B illustrate that neither I_{Ks} activated during depolarisation nor tail I_{Ks} on repolarisation was affected by 10 μM nifedipine, whereas both were inhibited by 100 μM nifedipine. Inspection of the records indicates that the time courses of currents in the presence of the drug were similar to those under control conditions.

The dependence of I_{Ks} inhibition on the concentration of nifedipine was determined by measuring the amplitudes of tail currents after depolarisations to +60 mV. Fig. 4C indicates that the steady-state data are well-described by the Hill equation with IC_{50} of 360 μM and coefficient of 0.97.

Tail I_{Ks}–V relationships determined from records such as those in Fig. 4A,B provided no clear indication that the

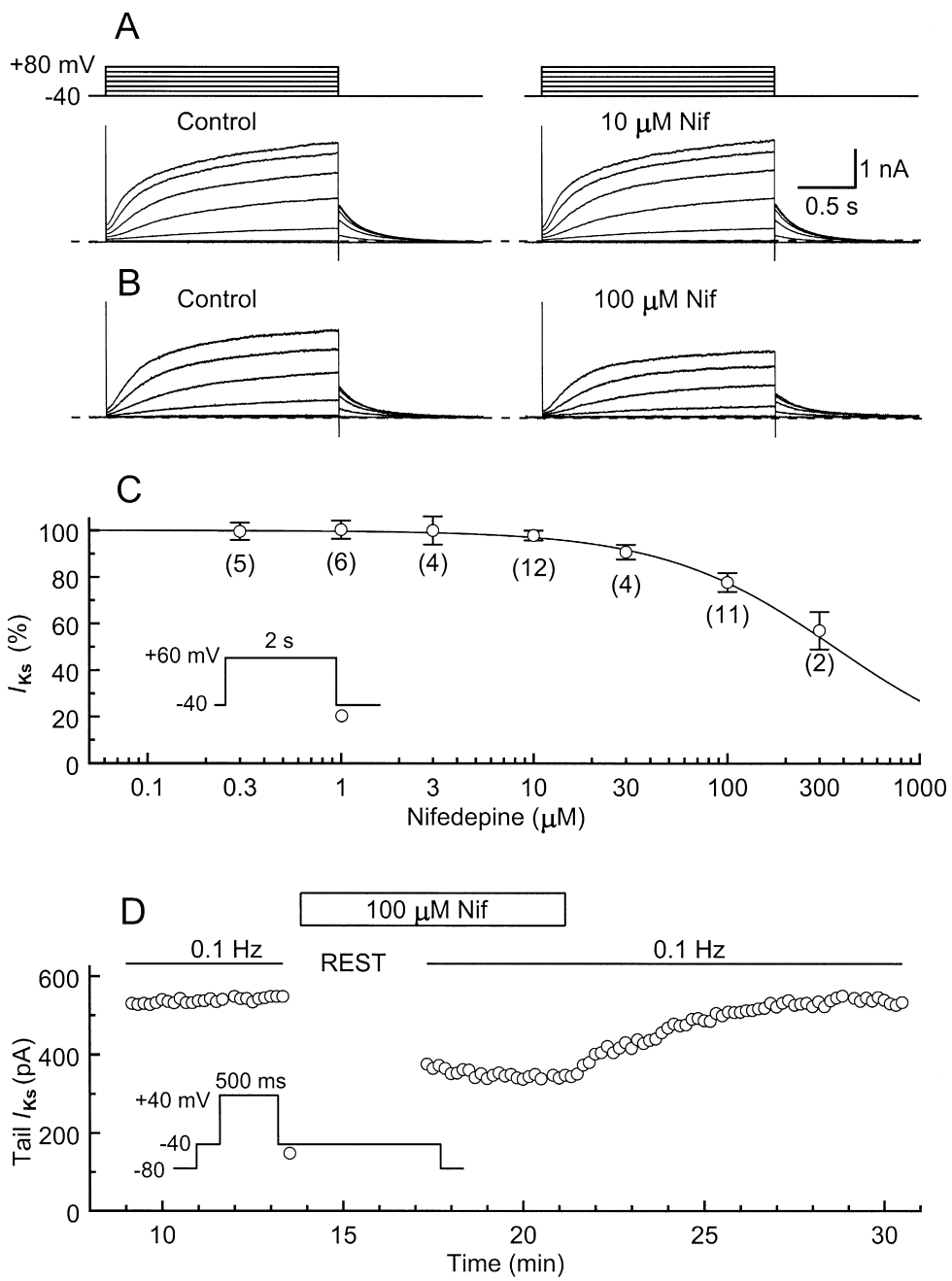

Fig. 4. Inhibition of I_{Ks} by nifedipine. (A,B) Records obtained before and 8–10 min after application of nifedipine to representative myocytes. The myocytes were bathed with K^+-, Ca^{2+}-free Cd^{2+} solution to suppress I_{Kr} and Ca^{2+}-dependent currents, and depolarised from −40 mV to more positive potentials for 2 s to activate large I_{Ks}. (C) Dependence of inhibition on the concentration of nifedipine. I_{Ks} was measured as the amplitude of tail I_K after 2-s pulses to +60 mV. The Hill equation fitting the data has an IC_{50} of 360 μM and coefficient of 0.97. The numbers of myocytes are shown in parentheses. (D) Near-maximal inhibition of tail I_{Ks} by 100 μM nifedipine on the first depolarisation to +40 mV after a 4-min rest at −80 mV in the presence of the drug.

degree of block was affected by the voltage of the depolarising pulse. To determine whether inhibition had a use-dependent component, myocytes were depolarised with 500-ms pulses at 0.1 Hz, and 100 μM nifedipine was applied shortly after the beginning of a 4-min rest period at −80 mV. The data in Fig. 4D indicate that inhibition on the first post-rest depolarisation was as large as that reached on subsequent depolarisations. In four experiments, tail I_{Ks} amplitudes on the first and 30th post-rest activations were 69 ± 4% and 68 ± 5% of predrug control, respectively. These values are significantly different than control, but not different from one another or from the value obtained from experiments in which regularly pulsed myocytes were treated with 100 μM nifedipine (77 ± 4%, $n = 11$: Fig. 4C).

4. Discussion

The results of the present study provide new information on the sensitivity of cardiac inward-rectifier and delayed-rectifier K^+ channels to inhibition by nifedipine. The major findings are discussed and compared with those of earlier studies on the actions of nifedipine on native and cloned cardiac and non-cardiac K^+ channels.

4.1. Effects on inwardly rectifying K^+ current

Although there have been no previous studies on the concentration-dependent effects of nifedipine on either cardiac I_{K1} or non-cardiac I_{K1}-like currents, Kass (1982) has previously reported that 10–100 μM concentrations of a related dihydropyridine (nisoldipine) was without effect on outward I_{K1} in cardiac Purkinje fibers. In the guinea-pig ventricular myocytes investigated here, nifedipine inhibited outward I_{K1} with an IC_{50} of 260 μM, and the degree of block appeared to be independent of voltage and of the direction of the current. Reversal occurred more slowly than reversal of block of delayed-rectifier current, an observation that has previously been made in regard to block of cardiac K^+ channels by clofilium analogues (Arena and Kass, 1988) and terodiline (Jones et al., 1999).

4.2. Comparison with earlier results on delayed-rectifier K^+ currents in non-cardiac cells

There have been numerous studies on the effects of nifedipine on delayed-rectifier K^+ currents in excitable and non-excitable cells, and in most cases the currents were inhibited with an IC_{50} lower than 40 μM. For the purpose of comparing these earlier results with those presented here, it is useful to divide the non-cardiac delayed-rectifier K^+ currents into a fast-activating slowly inactivating type, and a slowly activating non-inactivating type.

Fast-activating slowly inactivating delayed-rectifier K^+ currents are almost ubiquitous in non-cardiac cells and, without exception, appear to be sensitive to inhibition by dihydropyridine Ca^{2+} channel blockers. A sampling of the IC_{50} values determined from measurements of the peak amplitude of the current in various cell types is as follows: 4.6 μM nicardipine in rabbit small intestine smooth muscle cell membrane (Terada et al., 1987), ca. 5 μM nifedipine in *Aplysia* bag cell neurons (Nerbonne and Gurney, 1987), ca. 18 μM nifedipine in cultured rat brown fat cells (Pappone and Ortiz-Miranda, 1993) and in rat alveolar epithelial cells (Jacobs and DeCoursey, 1990), and ca. 35 μM nifedipine in guinea-pig small intestine enterocytes (Tatsuta et al., 1994) and guinea-pig outer hair cells (Lin et al., 1995). A common observation was that nifedipine markedly accelerated the apparent rate of inactivation, and this effect occurred with concentrations that were lower than those required to inhibit peak current. An interpretation of these findings is that nifedipine blocks open K^+ channels in a time-dependent manner (e.g., see Jacobs and DeCoursey, 1990; Tatsuta et al., 1994).

There have been fewer studies on the sensitivity of more slowly activating non-inactivating types of delayed-rectifier currents to nifedipine, and the results are far from consistent. For example, Nerbonne and Gurney (1987) found that this type of current in *Aplysia* bag cell neurons was inhibited with an IC_{50} of 4 μM, a value consistent with the IC_{50} estimated by Nishi et al. (1983) for this type of current in *Helix* neurons. On the other hand, Gola and Ducreux (1985) and Lukyanenko et al. (1995) reported that 80–100 μM nifedipine had no effect on this type of current in *Helix* neurons and cultured frog skeletal muscle myocytes, respectively.

4.3. Comparison with earlier results on cardiac delayed-rectifier K^+ currents

Previous studies on native and cloned cardiac K^+ channels indicate that at least two delayed-rectifier pathways in cardiac cells are blocked by nifedipine with an IC_{50} of 20 μM or less. In experiments on rabbit atrial myocytes, Gotoh et al. (1991) found that peak I_{to} was inhibited with an IC_{50} of 14 μM. Nifedipine also decreased peak I_{to} in rat ventricular myocytes, and accelerated the apparent rate of inactivation with IC_{50} near 5 μM (Jahnel et al., 1994). Fast-activating slowly inactivating I_{Kur}-type current in cell lines expressing hKv1.5 channels was also sensitive to nifedipine, with IC_{50} values of 19 and 6 μM for peak and late currents, respectively (Zhang et al., 1997).

The results of the present study on guinea-pig ventricular myocytes indicate that nifedipine inhibits both I_{Kr} and I_{Ks}, and that the IC_{50} values are near 275 and 360 μM, respectively. Although we are unaware of previous data on the sensitivity of I_{Kr} and I_{Ks} to nifedipine, it should be noted that Hume (1985) found that the related compound, nisoldipine, inhibited global I_K in frog atrial myocytes with an IC_{50} of 16 μM. More recently, Zhang et al. (1999) reported that I_{Kr}-type current carried by the human *ether-*

a-gogo-related gene HERG product was unaffected by lengthy exposures to 30 μM nifedipine. The latter result is in reasonable agreement with our finding that 30 μM nifedipine only inhibited 13 ± 3% of I_{Kr}.

In summary, the concentrations of nifedipine required for inhibition of I_{Kr} and I_{Ks} are one to two orders higher than those that inhibit two other types of cardiac delayed-rectifier K^+ current, i.e., I_{to} and hKv1.5. In regard to the latter currents, it has been proposed that their inhibition involves the binding of nifedipine molecules to open channels (Jahnel et al., 1994; Zhang et al., 1997). Although our results on the onset of I_{Ks} block after rest periods at negative potentials (Fig. 4D) raise the possibility that block is related to a binding of drug to closed channels, they are equally well explained by a mechanism that involves rapid binding (e.g., milliseconds) to open channels.

Acknowledgements

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References

Arena, J.P., Kass, R.S., 1988. Block of heart potassium channels by clofilium and its tertiary analogs: relationship between drug structure and type of channel blocked. Mol. Pharmacol. 34, 60–66.

Fleckenstein, A., 1983. History of calcium antagonists. Circ. Res. 52, 13–16.

Gola, M., Ducreux, C., 1985. D600 as a direct blocker of Ca-dependent K currents in *Helix* neurons. Eur. J. Pharmacol. 117, 311–322.

Gotoh, Y., Imaizumi, Y., Watanabe, M., Shibata, E.F., Clark, R.B., Giles, W.R., 1991. Inhibition of transient outward K^+ current by DHP Ca^{2+} antagonists and agonists in rabbit cardiac myocytes. Am. J. Physiol. 260, H1737–H1742.

Hume, J.R., 1985. Comparative interactions of organic Ca^{++} channel antagonists with myocardial Ca^{++} and K^+ channels. J. Pharmacol. Exp. Ther. 234, 134–140.

Jacobs, E.R., DeCoursey, T.E., 1990. Mechanisms of potassium channel block in rat alveolar epithelial cells. J. Pharmacol. Exp. Ther. 255, 459–472.

Jahnel, U., Klemm, P., Nawrath, H., 1994. Different mechanisms of the inhibition of the transient outward current in rat ventricular myocytes. Naunyn Schmiedeberg's Arch. Pharmacol. 349, 87–94.

Jones, S.E., Ogura, T., Shuba, L.M., McDonald, T.F., 1998. Inhibition of the rapid component of the delayed-rectifier K^+ current by therapeutic concentrations of the antispasmodic agent terodiline. Br. J. Pharmacol. 125, 1138–1143.

Jones, S.E., Kasamaki, Y., Ogura, T., Shuba, L.M., McCullough, J.R., McDonald, T.F., 1999. Inhibition of cardiac inward-rectifier K^+ current by terodiline. Eur. J. Pharmacol. 370, 319–327.

Kass, R.S., 1982. Nisoldipine: a new, more selective calcium current blocker in cardiac Purkinje fibers. J. Pharmacol. Exp. Ther. 223, 446–456.

Lin, X., Hume, R.I., Nuttall, A.L., 1995. Dihydropyridines and verapamil inhibit voltage-dependent K^+ current in isolated outer hair cells of the guinea pig. Hear. Res. 88, 36–46.

Lukyanenko, V., Katina, I.E., Nasledov, G.A., Terentyev, D.A., 1995. Pharmacological analysis of voltage-dependent potassium currents in cultured skeletal myocytes of the frog *Rana temporaria*. Gen. Physiol. Biophys. 14, 525–534.

Nerbonne, J.M., Gurney, A.M., 1987. Blockade of Ca^{2+} and K^+ currents in bag cell neurons of *Aplysia californica* by dihydropyridine Ca^{2+} antagonists. J. Neurosci. 7, 882–893.

Nishi, K., Akaike, N., Oyama, Y., Ito, H., 1983. Actions of calcium antagonists on calcium currents in *Helix* neurons. Specificity and potency. Circ. Res. 52, I53–I59.

Ogura, T., Shuba, L.M., McDonald, T.F., 1995. Action potentials, ionic currents and cell water in guinea pig ventricular preparations exposed to dimethyl sulfoxide. J. Pharmacol. Exp. Ther. 273, 1273–1286.

Pappone, P.A., Ortiz-Miranda, S.I., 1993. Blockers of voltage-gated K channels inhibit proliferation of cultured brown fat cells. Am. J. Physiol. 264, C1014–C1019.

Sanguinetti, M.C., Jurkiewicz, N.K., 1990. Two components of cardiac delayed rectifier K^+ current. Differential sensitivity to block by class III antiarrhythmic agents. J. Gen. Physiol. 96, 195–215.

Tatsuta, H., Ueda, S., Morishima, S., Okada, Y., 1994. Voltage- and time-dependent K^+ channel currents in the basolateral membrane of villus enterocytes isolated from guinea pig small intestine. J. Gen. Physiol. 103, 429–446.

Terada, K., Kitamura, K., Kuriyama, H., 1987. Blocking actions of Ca^{2+} antagonists on the Ca^{2+} channels in the smooth muscle cell membrane of rabbit small intestine. Pflügers Arch. 408, 552–557.

Triggle, D.J., Swamy, V.C., 1983. Calcium antagonists. Some chemical-pharmacologic aspects. Circ. Res. 52, I17–I28.

Zhang, S., Zhou, Z., Gong, Q., Makielski, J.C., January, C.T., 1999. Mechanism of block and identification of the verapamil binding domain to HERG potassium channels. Circ. Res. 84, 989–998.

Zhang, X., Anderson, J.W., Fedida, D., 1997. Characterization of nifedipine block of the human heart delayed rectifier, hKv1.5. J. Pharmacol. Exp. Ther. 281, 1247–1256.