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Electrophysiological basis for antiarrhythmic efficacy, positive inotropy and low proarrhythmic potential of (−)-caryachine

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1 (−)-Caryachine, isolated from the plant (*Cryptocarya chinensis*), increased the contractility of atrial and right ventricular strips and significantly suppressed the reperfusion arrhythmias in adult rabbit heart (ED_{50} = 1.27 μM).

2 Data obtained by the whole-cell voltage clamp technique has shown that (−)-caryachine causes a negative shift of the steady-state Na channel inactivation and a slower rate of recovery from inactivation. The maximal Na current amplitude decreased to 67±7%, 29±8% and 12±5% after 0.5, 1.5 and 4.5 μM (−)-caryachine, respectively.

3 This agent also had effects on the time- and voltage-dependent K currents. (−)-Caryachine markedly suppressed the 4-AP-sensitive transient outward current (I_{to}). However, it produced very little voltage-dependent shift in inactivation. After 0.5, 1.5 and 4.5 μM of the compound, the respective value of I_{to} elicited at +60 mV was 80±7%, 45±8% and 15±3%. At higher concentrations, the inward rectifier K current (I_{K1}) was also inhibited but to a much smaller extent. Its slope conductance after 0.5, 1.5 and 4.5 μM (−)-caryachine was reduced to 71±9%, 51±12% and 42±11%, respectively. The outward hump of inward rectification was not changed.

4 In contrast, the L-type Ca current was not significantly changed by (−)-caryachine.

5 Electrophysiological studies in perfused whole heart preparations revealed that (−)-caryachine increased the intra-atrial conduction interval and also prolonged the atrial refractory period. No proarrhythmic effects were induced during the infusion of this compound (up to 13.5 μM).

6 We conclude that (−)-caryachine predominantly blocks the Na and I_{to} currents. These changes alter the electrophysiological properties of the heart and terminate the induced ventricular arrhythmias. The relatively selective I_{to} inhibition, safety margin of I_{K1} suppression and lack of effect on $I_{Ca\text{-}L}$ will provide an opportunity to develop an effective antiarrhythmic agent with positive inotropy as well as low proarrhythmic potential.

Keywords: (−)-Caryachine; electrophysiology; ion currents; cardiac arrhythmia

Introduction

Medicinal plants have been used in traditional medicine in Oriental countries for hundreds of years. By using large-scale screening tests and electrophysiological studies, some derivatives of these medicinal plants have been shown to be promising antiarrhythmic, or positive inotropic agents (Su *et al.*, 1993; Young *et al.*, 1994; Wu *et al.*, 1994a). During one such large-scale screening test, (−)-caryachine, a compound isolated from natural plant (*Cryptocarya chinensis*) (Figure 1a) (Lu & Lan, 1966), mol.wt. 325 g, has been shown to increase the contractility of right ventricular and left atrial strips (Figure 1b and 1c). We have therefore evaluated its antiarrhythmic effects and electrophysiological actions. Our results define its effects on the ionic currents of cardiac myocytes, as well as its effects on the conduction system of isolated Langendorff-perfused hearts. The antiarrhythmic efficacy was demonstrated by its ability to convert ventricular arrhythmias which were induced by ischaemia-reperfusion of the isolated hearts. The proarrhythmic potential was examined using a standard pacing protocol and was shown to be minimal.

Methods

Adult (>3 months) New Zealand white rabbits were anaesthetized with intravenous injection of sodium pentobarbitone (30 mg kg^{-1}, i.v.) and given heparin (300 units kg^{-1}).

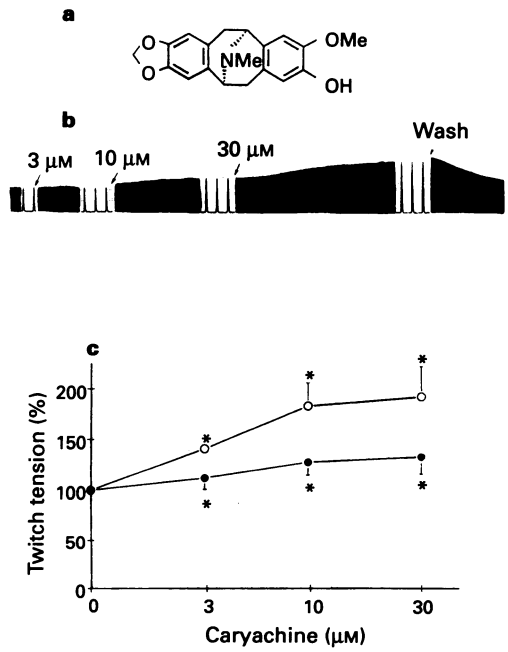

Figure 1 (a) The chemical structure of (−)-caryachine. (b) The contractility of the left atrial strip increased after the addition of (−)-caryachine. (c) Dose-response curve for changes in contractility of left atrial (○) and right ventricular (●) strips after (−)-caryachine. *P<0.05.

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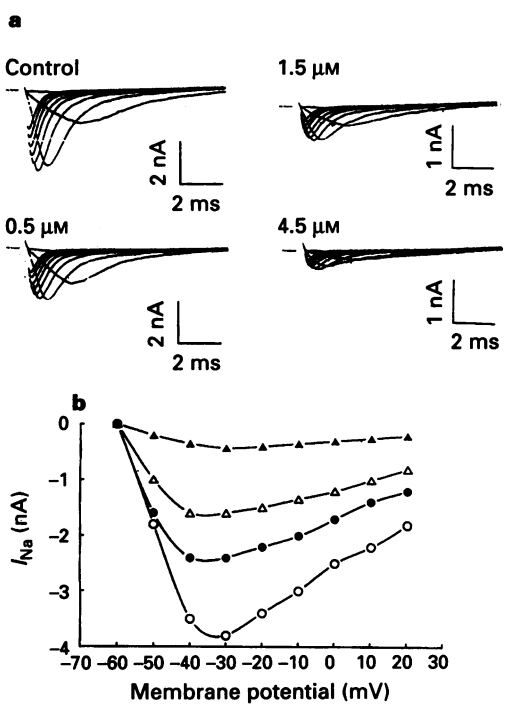

Figure 2 (a) Na currents were elicited from a holding potential of −80 mV as depolarizations from −60 mV to 20 mV in 10 mV steps. (−)-Caryachine decreased the Na currents. (b) The current-voltage relationship shows changes of Na currents after the addition of (−)-caryachine at 0.5 (●), 1.5 (△) and 4.5 μM (▲); control (○). Na currents were decreased but the threshold potential and the potential at which the maximal Na current was recorded remained unchanged.

Whole-cell voltage clamp recording

Cardiac myocytes were isolated as previously described (Mitra & Morad, 1985; Wu *et al.*, 1994a). Ionic currents were studied in whole-cell configuration at room temperature (25–27°C) (Hamill *et al.*, 1981). A Dagan 8900 patch/whole cell clamp fitted with 0.1 GΩ feedback resister in the headstage was used to voltage clamp the cell membrane potential. The total series resistance for the pathway between pipette interior and cell membrane was estimated from the cell capacitance and capacitance current decay and was about 4–5 mΩ. It was possible to compensate electronically for 60% of the voltage drop across the electrode produced by the current flow, leaving an uncompensated resistance of 1–2 MΩ. To lower the maximal amplitude of Na currents, I_{Na} was studied in a low Na^+ Tyrode solution ($[Na^+]$ = 54 mM, with NaCl replaced by N-methyl-D-glucamine) and dialysis of the cell with Na containing (10 mM) Cs^+ pipette solution. Results from experiments in which the estimated voltage error attributed to uncompensated R_s was less than 10 mV, i.e., a maximal current smaller than 5 nA were retained (Wu *et al.*, 1994a, b). Cells were exposed to each concentration of test drug for 7 min.

Intracardiac electrocardiogram recording

Animal preparation The heart including part of the superior and inferior vena cava was excised via thoractomy and the aorta was retrogradely perfused (Young *et al.*, 1989; Wu *et al.*, 1994a). A tungsten wire soldered to a silver-wire bipolar electrode was placed on an area near the apex of the triangle of Kochs to record the His bundle electrograms (HBE). The ventricular recording electrodes were placed on the epicardium of the right ventricular apex to obtain an easily recognizable T wave.

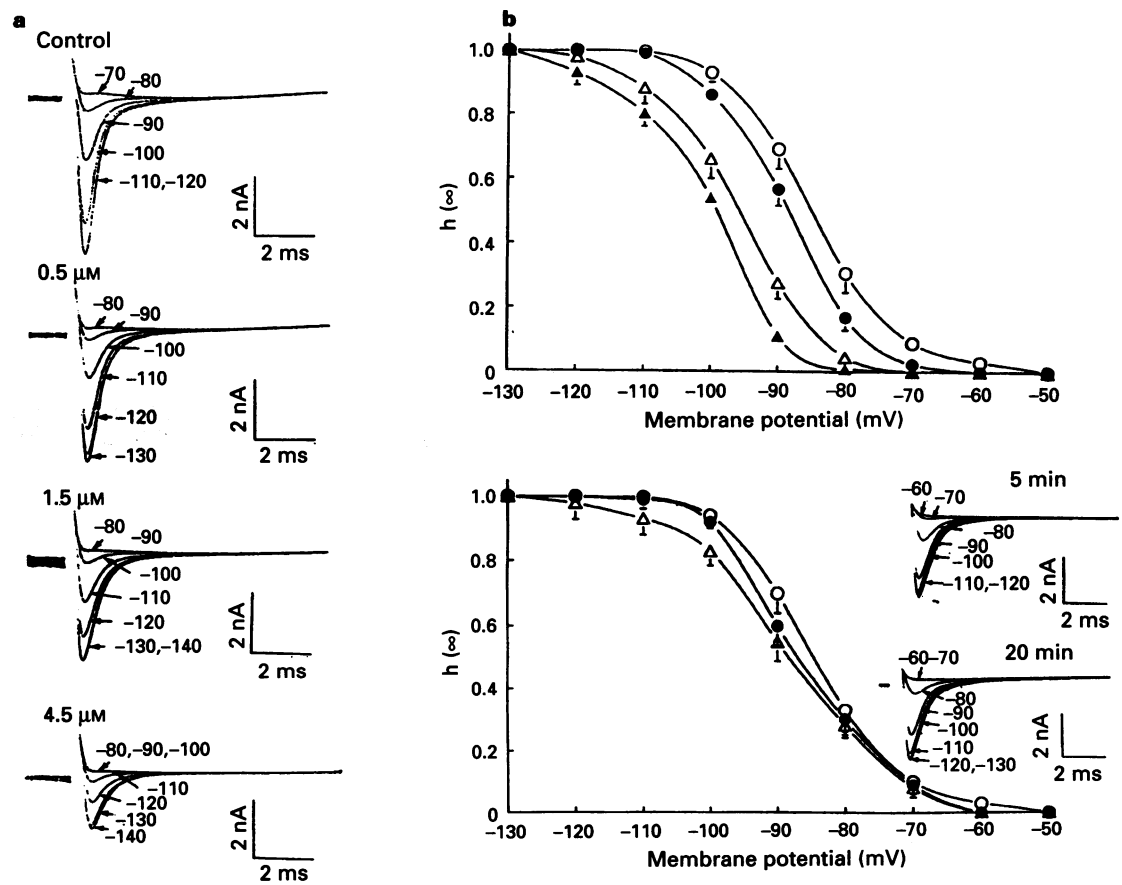

Figure 3 Modification of Na current after (−)-caryachine. (a) Steady-state voltage dependent-inactivation of I_{Na} was studied by altering the holding potentials for 1 s and then a depolarizing pulse to −20 mV. (b) (−)-Caryachine caused a hyperpolarizing shift of the steady-state inactivation curves (n = 7). This shift was statistically significant for the concentrations of 1.5 and 4.5 μM: (○) control; (●) 0.5 μM; (△) 1.5 μM; (▲) 4.5 μM. Alteration in the steady-state voltage dependent inactivation with time of the control is also shown in the lower panel (n = 4): (○) 5 min; (●) 10 min; (△) 20 min.

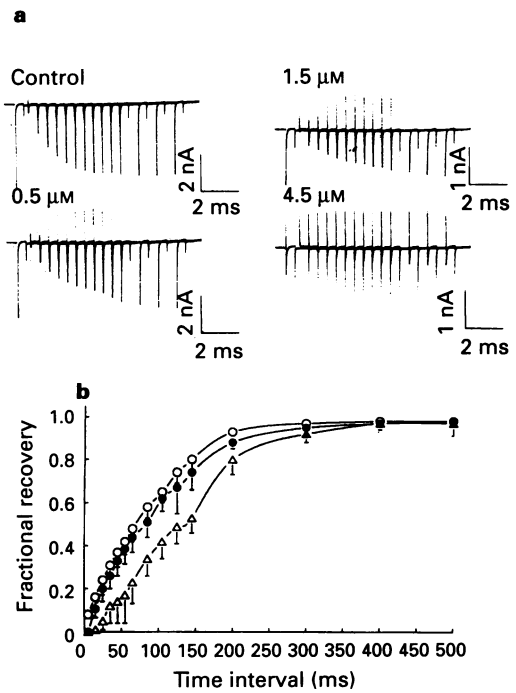

Figure 4 Recovery of Na channels from inactivation. Na currents were elicited by twin-pulse depolarization protocol. Cells were first depolarized to −20 mV for 10 ms from a holding potential of −80 mV. The kinetics of recovery was then defined by a second depolarization given at various time intervals after the first pulse. Ratios of the currents elicited by the second and first pulses reflected the fractions of Na channels which have recovered from inactivation. The changes were statistically significant at the concentration of 0.5 (●) and 1.5 μM (△) ($n=6$); (○) control. I_{Na} could frequently not be elicited after 4.5 μM (−)-caryachine, therefore the recovery time course at this concentration was not plotted.

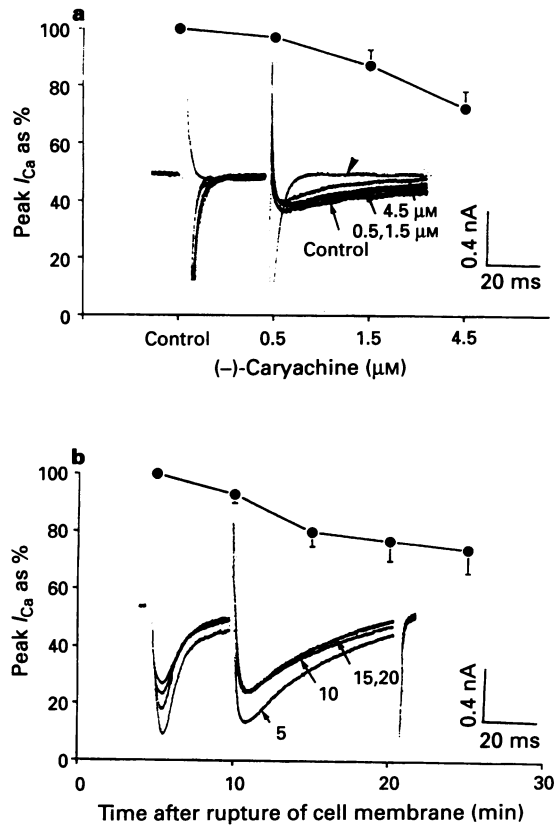

Figure 5 (a) The dose response curve for L-Ca current suppression by (−)-caryachine ($n=6$). The L-Ca currents were not significantly affected. *Insert*: A conditioning pulse to −40 mV was applied to inactivate the Na channel and 'T' type Ca channels, and then a depolarizing pulse to 0 mV of 80 ms duration was applied to elicit the peak L-Ca current. The last current trace (arrowhead) was recorded after the addition of 0.5 mM Cd^{2+} to eliminate the I_{Ca} completely. (b) Spontaneous rundown of the $I_{Ca\text{-}L}$ with the time after rupture of the cell membrane.

A pacing stimulus of 1 ms in duration and three times the diastolic threshold voltage was applied to the preparation. The high right atrial pacing electrode was placed on the epicardium near the junction of the superior vena cava and right atrium. The ventricular pacing electrode was placed on the pericardium near the right ventricular apex.

Experimental protocol

The protocol used for electrophysiological studies has been previously described and was performed according to standard methods (Josephson & Seides, 1993). The average of 4 stable cycle lengths of spontaneous heart beats was taken as the parameter of the pacemaker automaticity, which could be a sinus or an atrial pacemaker. Corrected QT interval was used as the parameter for monitoring ventricular repolarization. The right atrium was then paced at a constant rate which was slightly faster than the spontaneous heart rate. At this constant rate pacing, the intra-atrial conduction time (SA), AV nodal conduction time (AH) and His-Purkinje conduction time (HV) were measured.

Incremental right atrial pacing was used to determine the Wenckebach cycle length. Atrial extra-stimulation (S_1S_2) was performed to obtain the refractory periods of atrial, atrioventricular and His-Purkinje system. The ventricular effective refractory period (VERP) was similarly determined by a ventricular extrastimulation study protocol.

Induction and conversion of ventricular arrhythmia

A Langendorff-perfused heart model with constant perfusion pressure instead of constant flow was used (Curtis & Hearse, 1989). The electrograms were recorded from a low atrial and a ventricular recording electrode. Reperfusion ventricular arrhythmia was induced by ligation of the left coronary artery for 20–30 min before the release of the ligature. The antiarrhythmic effect of the compound was tested after arrhythmias had been induced and persisted for at least 5 min.

Drugs

(−)-Caryachine was isolated from *Cryptocarya chinensis* Hemsl. The sample for this study was recrystallized from acetone at 236°C. The purity was about 99% as analyzed by ^{1}H-n.m.r. and h.p.l.c.. The compound (stored at −20°C) was dissolved in dimethylsulphoxide as a 50 mM stock solution from which the test solutions in concentrations of 0.5, 1.5, 4.5 and 13.5 μM were prepared. Drugs were administered in a cumulative manner.

Solutions

Three basic solutions were used with the following compositions in mM: (1) Ca^{2+}-Tyrode: NaCl 137, KCl 5.4, $MgCl_2$ 1.1, $CaCl_2$ 1.8, HEPES 12, titrated with NaOH to pH 7.4; (2) Internal solution for filling the suction pipettes: KCl 120, NaCl 10, MgATP 5, K_2EGTA 10, $CaCl_2$ 1.5, HEPES 10, pCa, 6.8, titrated with KOH to pH 7.4. Internal solution containing 120 mM Cs^+ instead of K^+ was used for I_{Na} and I_{Ca} studies. Junctional potentials of both types of pipette were about 5–10 mV. (3) KB medium: taurine 10, glutamic acid 70, KCl 25, KH_2PO_4 10, dextrose 22, EGTA 0.5, titrated with KOH to pH 7.3.

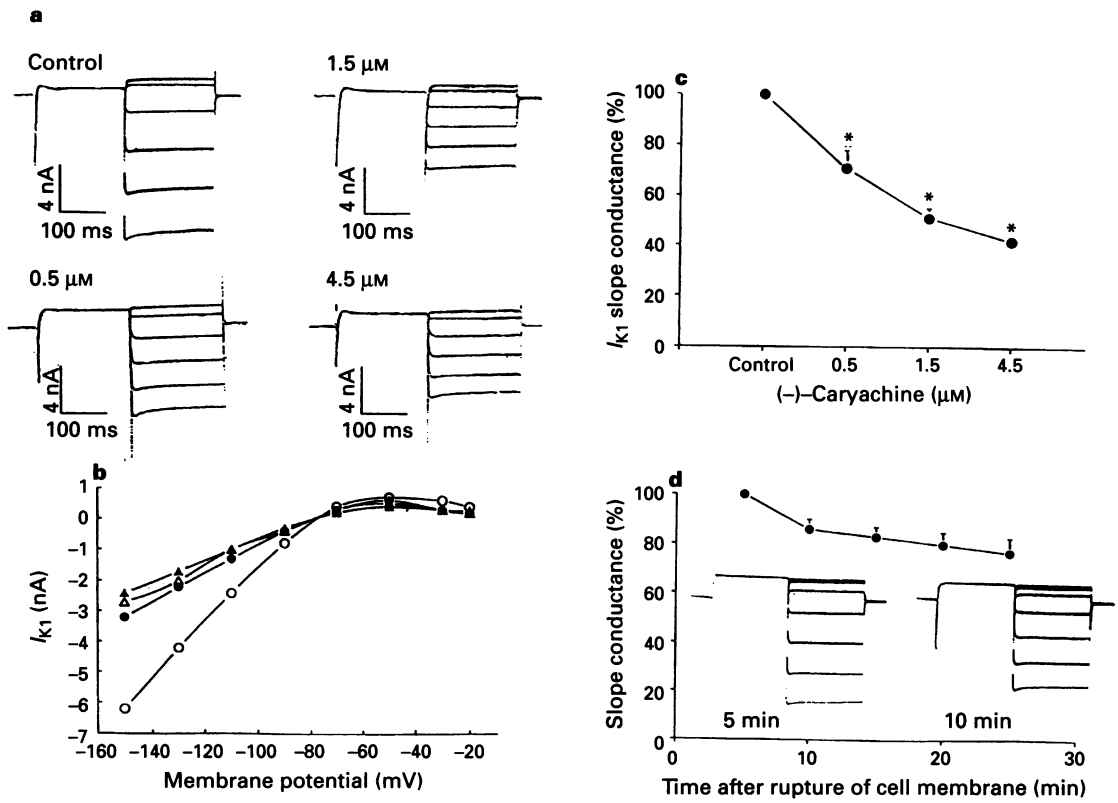

Figure 6 (a) (−)-Caryachine suppresses I_{K1}. The currents were elicited (−30 to −150 mV 20 mV steps) from a holding potential of −80 mV and a prepulse at −20 mV for 200 ms to fully deactivate the I_{K1} and inactivate the I_{Na}. Under these condition, I_{K1} could be satisfactorily studied without the I_{Na} contamination. The I_{K1} currents elicited at potentials more negative than −70 mV were decreased, but the outward hump (inward rectification) at the range from −60 to −20 mV was not modified. (b) The current-voltage relationship of I_{K1} after (−)-caryachine: (○) control; (●) 0.5 μM; (△) 1.5 μM; (▲) 4.5 μM. (c) The dose-response curve for I_{K1} supression by (−)-caryachine ($n=7$). (d) Spontaneous 'rundown' of the I_{K1} with time after rupture of the cell membrane ($n=4$).

Statistics

The data are expressed as mean ± s.d. for each parameter. A repeated-measures analysis of variance was used for data comparison.

Results

Ionic current modification

I_{Na} was elicited from a holding potential of −80 mV to depolarizing potentials ranging between −60 and 0 mV. Under control condition, I_{Na} was activated at the threshold potential of around −60 mV and attained its maximum around −30 mV. (−)-Caryachine blocked I_{Na} (Figure 2). The maximal Na current amplitude elicited from a holding potential of −80 mV decreased to 67 ± 7%, 29 ± 8% and 12 ± 5% ($n=8$) after the addition of (−)-caryachine at 0.5, 1.5 and 4.5 μM respectively. (−)-Caryachine blocked the Na channel by causing a negative shift of the voltage-dependent steady-state inactivation curves as well as a slower rate of recovery from inactivation (Figures 3 and 4).

Conventional L-type Ca currents were elicited after application of a prepulse to −40 mV to inactivate the Na and 'T' type Ca channels. A time-dependent reduction of Ca currents due to the 'rundown' phenomenon was observed during the initial 10 min access of the patch pipette to the interior of the cells. Therefore, experiments were performed only on those cells with stable Ca currents 15 min after cell rupture. The Ca currents were not significantly affected by (−)-caryachine (Figure 6). Peak Ca currents elicited at the potential of 0 mV were 97 ± 6, 87 ± 15 and 72 ± 16% after 0.5, 1.5 and 4.5 μM of (−)-caryachine ($n=6$).

As reported by Giles *et al.*, the delayed outward K current was found to be very small in both rabbit atrial and ventricular cells (Giles & Von Ginneken, 1985; Giles & Imaizumi, 1988). Therefore, only the I_{K1} and I_{to} were studied. (−)-Caryachine decreased the I_{K1} currents. The outward hump recorded between the voltage range from −50 to −20 mV was not significantly affected (Figure 6). Its slope conductance measured between the membrane potential −70 and −110 mV after 0.5, 1.5 and 4.5 μM of (−)-caryachine was reduced to 71 ± 9, 51 ± 12 and 42 ± 11% respectively ($n=7$).

(−)-Caryachine markedly decreased the current peak and accelerated the inactivation of I_{to} (Figure 7). The area under the current curve elicited at 60 mV was calculated to estimate the total charge through the I_{to} channels after a baseline was obtained by rapid depolarization to fully inactivate I_{to}. The calculation by area provides a qualitative description of the changes in both the current peaks and the rate of inactivation. The integral of the curves decreased to 80 ± 7%, 45 ± 8% and 15 ± 3% ($n=8$) after 0.5, 1.5 and 4.5 μM (−)-caryachine respectively. Voltage-dependent inactivation of the I_{to} was studied further. After (−)-caryachine, only a small left-shift of the voltage-dependent inactivation of the I_{to} was noted (Figure 8).

Conduction system modification

Modifications in the electrophysiological properties of the cardiac conduction system after (−)-caryachine are summarized in Table 1. The effects up to the concentration of 4.5 μM (−)-caryachine were very small; we therefore increased the concentration to 13.5 μM. (−)-Caryachine caused a dose-dependent prolongation only in the intra-atrial conduction interval (Figure 9). The conduction interval through the atrioventricular node was not affected. Additionally, (−)-caryachine increased the effective refractory periods of the

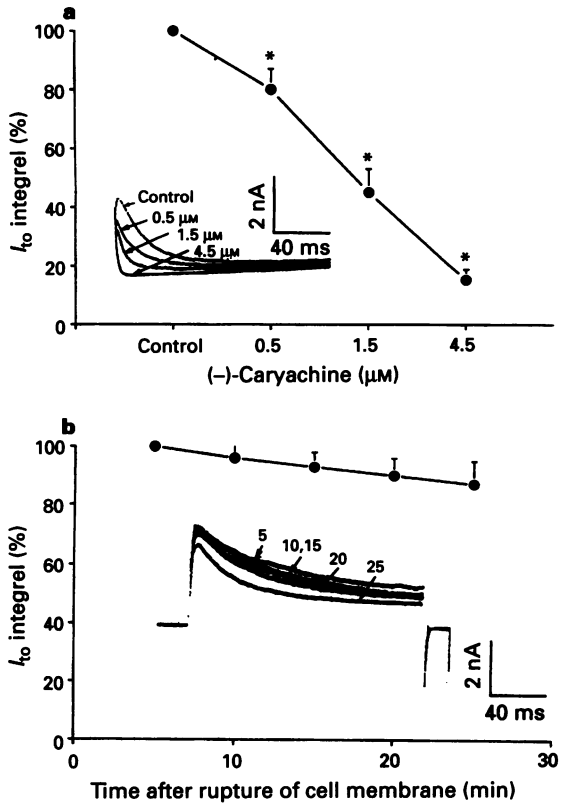

Figure 7 (a) Dose-response curve for I_{to} suppression by (−)-caryachine ($n=8$). *Insert*: I_{to} was studied in the presence of 0.5 mM $CoCl_2$. Repetitive depolarization to 60 mV from a holding potential of −80 mV at a slow stimulation frequency of 0.1 Hz was used to ensure complete recovery of these currents from their inactivation state. After the addition of 4.5 μM (−)-caryachine, most of the current was suppressed. $^*P<0.05$. (b) Spontaneous 'rundown' phenomenon of I_{to} with time. Insert was current traces recorded at 5, 10, 15, 20 and 25 min after rupture of cell membrane.

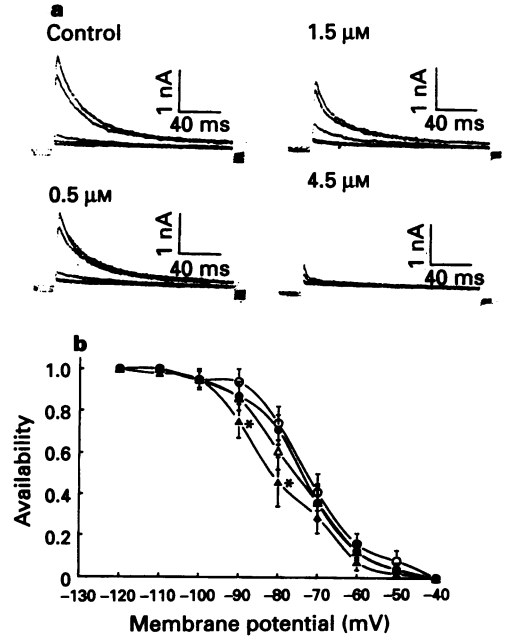

Figure 8 Steady-state voltage dependent-inactivation of I_{to} was studied by altering the holding potentials for 1 s and then applying a depolarizing pulse to +60 mV at a stimulation frequency of 0.1 Hz. Only after the addition of 4.5 μM (−)-caryachine, a small degree of left-shift in the voltage-dependent inactivation curve was observed ($n=6$): (○) control; (●) 0.5 μM; (△) 1.5 μM; (▲) 4.5 μM. $^*P<0.05$.

atrium, and to a less degree, the effective refractory periods of the His-Purkinje system and the ventricle. An example of (−)-caryachine-induced changes in the refractoriness of atrioventricular node was shown (Figure 10). At higher concentration (13.5 μM) of (−)-caryachine, a small effect on the refractoriness of the atrioventricular node was observed. The basic cycle length and corrected QT interval were not significantly changed. No new arrhythmias were induced during the perfusion of (−)-caryachine, as judged by a standard pacing protocol.

Antiarrhythmic efficacy

At a concentration of 0.5 to 4.5 μM, (−)-caryachine could convert a polymorphic ventricular tachycardia induced by ischaemia-reperfusion experiment model (Figure 11a, b). Out of 19 episodes of ventricular tachycardia induced by ischaemia-reperfusion, (−)-caryachine 0.5 μM converted the tachyrhythmia to normal sinus rhythm in 3 instances, 1.5 μM converted 11 of the remaining 16 episodes and 4.5 μM converted four of the other five episodes. For the one episode of refractory tachyrhythmia, 13.5 μM of (−)-caryachine still

Table 1 Dose-related effects of (−)-caryachine on the conduction system of rabbit isolated heart

		Caryachine (μM)				
	Control	*0.5*	*1.5*	*4.5*	*13.5*	*Wash*
BCL	100±0 (n=8)	101±6	99±7	101±6	103±7	104±6
SA	100±0	100±2	102±6	110±10	125±15	98±6
AH	100±0	99±6	98±5	100±5	101±7	96±5
HV	100±0	100±5	101±6	106±10	117±19	103±18
QTc	100±0	102±4	99±7	105±12	106±11	102±6
WCL	100±0	96±10	95±12	94±15	95±13	97±11
AERP	100±0	100±10	105±14	122±29	129±15	101±17
AVERP	100±0 (n=5)	101±9	99±7	101±12	107±18	98±12
HPERP	100±0 (n=6)	100±3	101±3	101±4	102±4	96±5
VERP	100±0	101±9	98±12	106±14	115±14	93±11

Data were obtained from 9 experiments respectively and are expressed as percentage of the control values (mean ± 1 s.d). Numbers in the parentheses indicate the numbers of experiment measurements for the parameters (BCL, HPERP and AVERP) which sometimes were limited by the physiological properties. Abbreviations: BCL: basic cycle length; SA: sinoatrial conduction interval; AH: atrio-His bundle conduction interval; HV: His-ventricular conduction interval; QTc: corrected QT interval; WCL: Wenckebach cycle length; AERP: atrial effective refractory period; HPERP: His Purkinje system effective refractory period; AVERP: AV nodal effective refractory period; VERP: ventricular effective refractory period.

could not convert the arrhythmia. The dose-response curve for arrhythmia conversion showed an ED_{50} of 1.27 μM (Figure 11b).

Discussion

In this study, we have demonstrated positive inotropy as well as a very significant antiarrhythmic efficacy of (−)-caryachine. The ED_{50} for conversion of arrhythmias occurred at low concentrations and the range of effective concentration was wide. No new arrhythmias were induced even at a concentration about 10 fold above the ED_{50}. (−)-Caryachine exerts its action via modifiction of mainly I_{Na} and I_{to}, and although there may be small changes in I_{K1}, also. These actions were similar to those found for class I antiarrhythmic agents, but were unique in the relatively selective I_{to} suppression, safety margin of I_{K1} suppression and minimal inhibition on I_{Ca}.

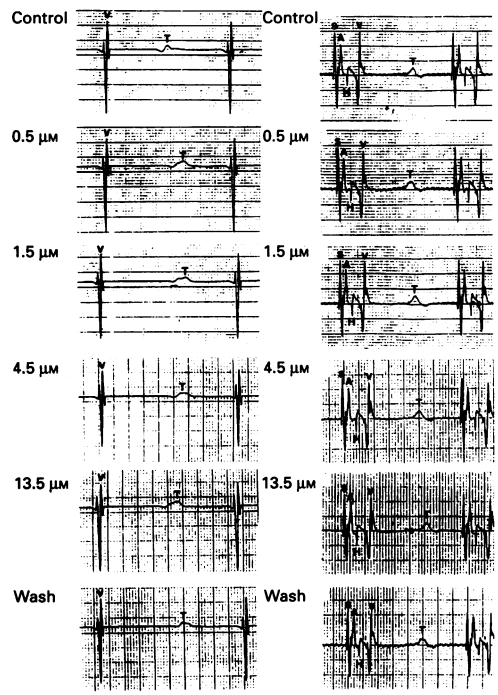

Figure 9 Representative ventricular electrogram recorded during normal sinus rhythm (a) and His bundle electrograms recorded during atrial pacing at 400 ms (b) after (−)-caryachine. A: atrial depolarization; H: His bundle depolarization; S: stimulation artifact; T: ventricular repolarization; V: ventricular depolarization. The paper speed was 100 mm s^{-1}.

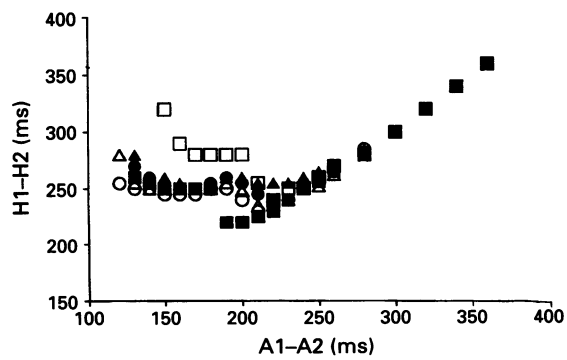

Figure 10 The modification of atrioventricular nodal properties shown by plotting the curve which related the H_1H_2 and A_1A_2. Only at very high concentrations of (−)-caryachine, were H_1H_2 responses to extrastimulation earlier than the relative refractory period of the AV node shifted upward: (○) control; (●) 0.5 μM; (△) 1.5 μM; (▲) 4.5 μM; (□) 13.5 μM; (■) wash. Atropine (1 μM) and atenolol (1 μM) were added to the control and (−)-caryachine-containing Tyrode solution, but not the wash Tyrode solution

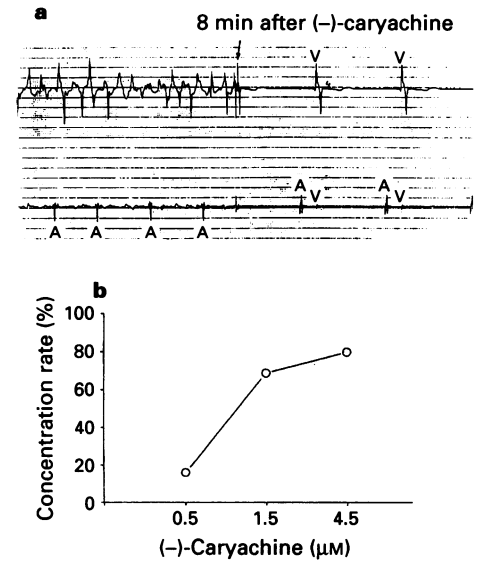

Figure 11 (a) A polymorphic ventricular tachycardia induced by ischaemia-reperfusion was converted to normal sinus rhythm 8 min after (−)-caryachine. Upper panel shows the ventricular electrogram. The electrogram of the lower panel was recorded at lower right atrium and shows the atrial (A) and ventricular depolarization (V). The paper speed was 100 mm s^{-1}. (b) The proportion of arrhythmias converted by (−)-caryachine at various concentrations is plotted against the drug concentration.

Most class I antiarrhythmic agents cause a use-dependent inhibition of I_{Na}, a slower recovery of Na channels from their inactivation state and a negative shift of the voltage-dependent inactivation curve of I_{Na} (Campbell 1992; Carmeliet & Saikawa 1982; Clarkson *et al.*, 1988; Nattel 1991; 1993; Grant & Wendt 1992; Tamargo *et al.*, 1992). In this study (−)-caryachine had been shown to block the Na channel in a similar way.

In rabbit atrial cells, I_{to} is responsible for the early repolarization phase of the action potential (Nakayama & Irisawa, 1985; Clark *et al.*, 1988). In human atrial and ventricular myocytes, the presence of I_{to} as well as its role in the repolarization process had been well demonstrated (Escande *et al.*, 1987; Heidbuchel *et al.*, 1990; Nabauer *et al.*, 1993). Therefore, an I_{to} suppression will increase the refractoriness of atrial and ventricular tissue. Such modification in both atrial and ventricular electrophysiological properties help to convert a wide variety of arrhythmias in human. It is known that some class I and class III antiarrhythmic agents exert part of their antiarrhythmic effects by suppressing K outward currents, which prolongs the action potential duration and thereby increases the refractoriness of the conduction system (Gwilt *et al.*, 1991; Hondeghem 1992; Hondeghem & Katzung, 1987; Imaizumi & Giles 1987; Lynch *et al.*, 1992; Noble, 1992; Singh & Nademanee 1985). However, none of these antiarrhythmic agents exhibit specificity in their effects on K channel blockade. A specificity in K channel blockade had been suggested to be associated with a lower proarrhythmic potential (Colatsky *et al.*, 1990). As shown in our results, (−)-caryachine blocked preferentially the I_{to} rather than the I_{K1}, and therefore could be considered as an antiarrhythmic agent with a relative specificity in K channel blockade. This could be further validated by the observation that (−)-caryachine did not significantly prolong the corrected QT intervals. An antiarrhythmic agent which blocks the delayed

outward K current and the I_{K1} commonly prolongs the corrected QT interval (Carmeliet 1993a). Therefore, a specificity in K channel blockade for (−)-caryachine is suggested.

In diseased human atrial tissue, a protective role of I_{to} has been described (Escande *et al.*, 1987). The I_{to} can overlap the I_{Ca} and prevent the firing at foci of abnormal automaticity. Then, it may be suggested that the marked I_{to} suppression along with a minimal I_{Ca} inhibition by (−)-caryachine could cause new arrhythmias. However, we have not observed any new arrhythmias induced by standard pacing protocols after (−)-caryachine even at a concentration up to 13.5 μM in both normal and ischaemia-reperfusion cardiac preparation.

The physiological role of I_{K1} is to maintain the resting membrane potential and to accelerate the terminal phase of phase 3 repolarization (Carmeliet, 1993b). Drugs that inhibit the I_{K1} are more likely to increase the diastolic membrane resistance and the resting length constant (Arnsdorf 1989; Colatsky *et al.*, 1990). Consequently, the extent of electrotonic interactions between cells would be increased and a given current will produce a larger voltage change. Cells may be more susceptible to the depolarizing influence of adjacent tissues. Such influence may favour the appearance of new arrhythmias by slowing conduction through inactivation of the Na channels and causing abnormalities in the repolarization time course (Arnsdorf 1989; Colatsky *et al.*, 1990). However, if the I_{K1} was only modestly decreased, the action potential upstroke could be spread to a greater distance, thereby facilitating the conduction. (−)-Caryachine decreased modestly the I_{K1} at the ED_{50} for its antiarrhythmic efficacy, and most importantly the inhibition was not enhanced further at higher concentration. In this way, (−)-caryachine may also offer some antiarrhythmic effect through a weak to moderate I_{K1} inhibition, and will not have a tendency to produce proarrhythmic activity by marked I_{K1} suppression (Rees & Curtis, 1993).

The positive inotropy of (−)-caryachine, another important feature of this compound, was attributed to the I_{to} inhibition along with a minimal I_{Ca} suppression by (−)-caryachine. The I_{to} inhibition would slow the initial repolarization or spike potential, and result in a large net inward current (Carmeliet, 1993b). This net balance between I_{to} and I_{Ca} may change the action potential configuration and increase the contractility of the myocardium (Maylie & Morad, 1984). Such positive inotropy is important especially in dealing with patients with heart failure. At present, digoxin is the only antiarrhythmic agent well documented to be associated with positive inotropy.

In conclusion, we have identified a significant antiarrhythmic efficacy for (−)-caryachine which was isolated from natural plants. The antiarrhythmic efficacy is linked with positive inotropy. Additionally, a relative specificity in K channel blockade as well as a safety margin in I_{K1} inhibition may guard the development of new arrhythmias. Therefore, we suggest that (−)-caryachine is a very promising drug for the treatment of cardiac arrhythmias.

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