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Effects of *m*-nisoldipine and nisoldipine on electric activity of human atrial tissue

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ABSTRACT Using intracellular microelectrode technique and microcomputer analyzing system, the effects of *m*-nisoldipine (*m*-Nis) and nisoldipine (Nis) on spontaneous electric activity of human atrial tissue were studied. APA and V_{max} were remarkably decreased by *m*-Nis (0.25 and 1.25 μmol · L^{-1}) and Nis (0.25 μmol · L^{-1}). RPF was also greatly decreased as a result of inhibition in VDD. The inhibitory effects of *m*-Nis on transmembrane potentials were less than those of Nis at equal concentration (0.25 μmol · L^{-1}). Neither MDP nor APD_{90} was affected by *m*-Nis and Nis.

KEY WORDS *m*-nisoldipine; nisoldipine; heart atrium; microelectrode; action potentials

Human right atrial specialized fibers develop spontaneous phase 4 depolarization and automatic rhythm[1,2]. Verapamil, diltiazem, and nisoldipine (Nis)[2-4] remarkably decreased the spontaneous activity. The effects of *m*-nisoldipine (*m*-Nis) on human atrial electrical activity have not yet been reported. The purpose of this study was to examine the effects of *m*-Nis and Nis on the electric activity of human atrial fibers.

MATERALS AND METHODS

The right atrial tissue was obtained from the hearts of patients undergoing corrective surgery. The patients aged 3-18 a (8 ± *s* 5 a) were suffered from atrial septal defect (18) or ventricular septal defect (14) and with no evidence of atrial dysfunction, congestive heart failure, rheumatic heart disease. Patients receiving cardioactive drugs (digitalis, calcium channel blockers, β-adrenergic blocker) were excluced from this experiment. At surgery, approximately 1 cm^2 of right atrial appendage was removed from the right atrium as a part of the routine cannulation procedure for cardiopulmonary bypass. The tissue removed was immediately immersed in iced Tyrode's solution containing (mmol · L^{-1}): NaCl 149, KCl 4.7, $CaCl_2$ 0.5, Tris 10, glucose 10 (pH 7.3-7.4). The tissue was perfused with Tyrode's solution kept in 35℃ and equilibrated with 100% O_2.

Preparations were driven by electrical pulses (1 Hz, 1 ms, and 1.5 times of the threshold) provided by electrical stimulator (SEN-3201) through a pair of bipolar electrodes. The autonomacity was usually induced so long as the driving pulses were discontinued[1,2].

The tissues were impaled with KCl (3 mol · L^{-1})-filled glass microelectrodes having tip resistances of 10-25 MΩ. Transmembrane signal from the recording microelectrode was amplified by an amplifier (MEZ-8201) and monitored with an oscilloscope. The amplified signal was fed to the microcomputer and the parameters such as maximal diastolic potential (MDP), amplitude of action potential (APA), maximal rate of depolarization in phase 0 (V_{max}), velocity of diastolic (phase 4) depolarization (VDD), rate of pacemaker firing (RPF) and duration of 90% repolarization (APD_{90}) were analyzed automatically[5].

The experiment began after the prepara-

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tion had been equilibrated in the perfusate for 30 min and stable transmembrane potentials were recorded. The solvent and resource of *m*—Nis and Nis were previously described[6]. Measurements were made at the end of 20—min perfusion with Tyrode's solution containing solvent or different concentrations of *m*—Nis and Nis..

All values were expressed as $\bar{x} \pm s$ and the data were analysed using *F* test.

RESULTS

Control electrophysiological characteristics Stable spontaneous electric activity occurred following the cessation of a series of stimuli. Parameters of transmembrane potential in the control ($n = 14$) group were MDP 53 ± 4 mV, APA 60 ± 5 mV, V_{max} 9.4 ± 1.0 mV · s^{-1}, VDD 14 ± 5 mV · s^{-1}, RPF 59 ± 7 bpm and APD_{90} 169 ± 10 ms. The spontaneous rhythm was stable for at least 2.5 h in most of the preparations (Fig 1).

Effects of *m*—Nis and Nis *m*—Nis 0.05 μmol · L^{-1} showed no effect on APA, but V_{max} was significantly reduced. Both APA and V_{max} were reduced markedly by Nis 0.25 and *m*—Nis 1.25 μmol · L^{-1}. The depolarization was inhibited by *m*—Nis in concentration—dependent manner, and such an effect was less than that of Nis at equal concentration (0.25 μmol · L^{-1}). MDP and APD_{90} showed no significant change at any concentration of *m*—Nis and Nis used in the experiment (Fig 1, Tab 1). RPF and VDD were markedly depressed by *m*—Nis 0.25, 1.25, and Nis 0.25 μmol · L^{-1}. The decreases in RPF and VDD by *m*—Nis were less than those by Nis at equal concentration (0.25 μmol · L^{-1}). The inhibitory effect on VDD was more pronounced as the concentrations of *m*—Nis increased. The change of RPF was parallel to that of VDD (Fig 1, Tab 1). In 4 preparations, the spontaneous rhythm was eliminated by superfusion with Tyrode's solution containig *m*—Nis 1.25 μmol · L^{-1} for 25 to 40 min (Fig 1).

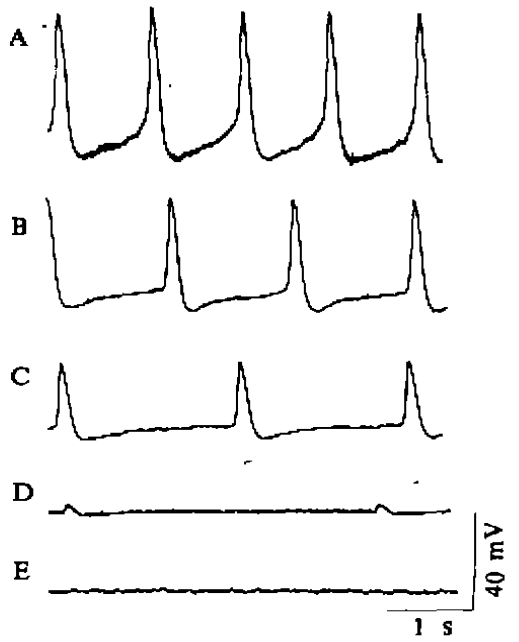

Fig 1. Effects of *m*—nisoldipine on spontaneous electrical activity of a preparation of human right atrial fiber. A) control; B) 0.25 μmol · L^{-1}; C) 1.25 μmol · L^{-1}; D) 30 min after 1.25 μmol · L^{-1}; E) cessation of spontaneous rhythm by superfusion with 1.25 μmol · L^{-1} for 35 min.

DISCUSSION

The results showed that *m*—Nis and Nis greatly decreased VDD at concentrations which did not affect the MDP, and the change in RPF was accompanied by a decrease in the VDD. Therefore, the inhibitory effects of these drugs on RPF may be mainly attributed to the reduction in VDD. These findings were consistent with those reported for verapamil[2,3]. Our previous results demonstrated that elevation of calcium concentration in perfusate partially antagonized the inhibitory effects of *m*—Nis and Nis on VDD in pacemaker cells of sinoatrial node in rabbit[7]. It is reasonable to consider the possibility that

Tab 1. Effects of *m*-nisoldipine and nisoldipine on slow response action potential of human right atrial tissue. $\bar{x} \pm s$. $^{*}P>0.05$, $^{**}P<0.05$, $^{***}P<0.01$ *vs* solvent; $^{+}P>0.05$, $^{++}P<0.05$, $^{+++}P<0.01$ *vs* *m*-Nis at equal concentration.

Drug / μmol · L^{-1}		*n*	MDP / mV	APA / mV	V_{max} / mV · s^{-1}	VDD / mV · s^{-1}	RPF / bpm	APD_{90} / ms
Solvent		6	51 ± 3	62 ± 3	8.8 ± 0.9	13.2 ± 3.6	62 ± 8	171 ± 13
m-Nis	0.05	6	50 ± 4*	61 ± 5*	9.2 ± 0.6*	12.0 ± 2.1*	56 ± 7*	170 ± 11*
	0.25	6	52 ± 5*	60 ± 3*	7.4 ± 0.6**	5.3 ± 0.9**	38 ± 7**	165 ± 12*
	1.25	5	49 ± 3*	51 ± 5**	5.1 ± 0.8***	2.1 ± 0.7***	14 ± 6***	164 ± 9*
Nis	0.25	5	50 ± 5^{+}	52 ± 4^{***+++}	6.5 ± 0.7^{***++}	4.0 ± 0.6^{***++}	29 ± 4^{***++}	167 ± 8^{+}

the inhibitory effects of *m*-Nis and Nis on VDD of human atrial tissue might be resulted from their blocking action on calcium influx.

The fact that the inhibitory effects of *m*-Nis on APA, V_{max}, VDD, and RPF in human atrial tissue were less than those of Nis at equal concentration, was in accordance with the results obtained from sinoatrial node of rabbit[7]. Kass[8] reported that Nis is a potent and more specific calcium current blocker without inhibition of current (i_x, delayed rectifier) responsible for repolarization in cardiac Purkinje fibers. The present results that *m*-Nis and Nis fail to show effect on APD_{90} have provided evidence that *m*-Nis, like Nis, have no effect on i_x for repolarization.

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间尼索地平及尼索地平对人心房肌电活动影响

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提要 采用细胞内微电极技术和微机分析系统，观察间尼索地平(*m*-Nis)和尼索地平(Nis)对人心房肌自发电活动的影响。*m*-Nis (0.25 和 1.25 μmol · L^{-1})和 Nis (0.25 μmol · L^{-1})可显著抑制 APA 和 V_{max}，通过抑制 VDD 也可显著减慢 RPF。*m*-Nis 对跨膜动作电位的抑制作用较等浓度 Nis 为弱。*m*-Nis 和 Nis 均不影响 MDP 和 APD_{90}。

关键词 间尼索地平；尼索地平；心房；微电极；动作电位