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Electrophysiological effects of cimetidine on rabbit myocardium

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ABSTRACT Effects of cimetidine (Cim) were studied electrophysiologically on fast action potential (AP) in rabbit papillary muscle and slow AP in pacemaker cell of rabbit sinoatrial node (SAN) as well as on atrioventricular (A-V) conduction in anesthetized rabbit. Cim (0.01, 0.1, 1, and 2 mmol · L^{-1}) induced prolongations of AP duration (APD) and effective refractory period (ERP), slowing down of the maximal rate of rise of phase 0 (V_{max}) and of the slope of phase 4 depolarization (SP_4), and a decrease of AP amplitude (APA) in concentration-dependent manners. Cim (100 mg · kg^{-1} iv) prolonged the A-V conduction. The results suggest that Cim, like quinidine, shows a membrane stabilizing effect, which may be the electrophysiological basis of the anti-arrhythmic effect of Cim.

KEY WORDS cimetidine; electrophysiology; action potentials; papillary muscles; sinoatrial node; electrocardiography

Animal experiments showed that Cim has several anti-arrhythmic effects[1]. There has been also a clinical report on the anti-arrhythmic effect of Cim[2]. Electrophysiological effects of Cim on guinea-pig myocardium[3] and dog Purkinje fiber (Zhang K, *et al. News Commun Chin Pharmacol Soc* 1984; 1: 136-7) were also observed in a few experiments. Our purpose is to investigate the influences of Cim on fast action potential (AP) in rabbit papillary muscle and slow AP in pacemaker cell of rabbit sinoatrial node (SAN) as well as in atrioventricular (A-V) conduction of anesthtized rabbit.

MATERIALS AND METHODS

Recording of AP in papillary muscle and SAN pacemaker cells New Zealand rabbits of either sex weighing 1.8 ± *s* 0.2 kg were stunned by a blow to the head. The hearts were quickly immersed in modified Tyrode solution, in which the papillary muscle of right ventricle and SAN preparation were excised. The solution contained (mmol · L^{-1}): NaCl 136.8; KCl 5.4; $MgCl_2$ 1.05; $CaCl_2$ 1.8; $NaHCO_3$ 1.2; glucose 11.0; Tris 5.0 and ventilated with O_2 (37 ± 1 ℃, pH 7.4 ± 0.05). The preparation were pinned to the silicone rubber bottom of a tissue chamber (3 ml) and purfused with Tyrode solution at a rate of 20 ml · min^{-1} for at least 60 min before recording the AP.

The papillary muscle was driven electrically with rectangular pulses of 3 ms duration and double the threshold intensity at a rate of 1 Hz (Nihon Kohden SEN-7103 stimulator, SS-102J isolator). A premature stimulus of 4-fold threshold intensity was inserted after each 8 normal pulses and the time interval between premature and normal stimuli was gradully shortened. The shortest interval to produce AP was the effective refractory period (ERP).

AP was recorded with conventional glass microelectrodes filled with KCl 3 mol · L^{-1} (DC resistance 10-30 MΩ). AP was guided into a microelectrode amplifier (Nihon Kohden MEZ-8201) through an Ag-$AgCl_2$ wire. An electronic differentiator was used to differentiate the AP. AP and maximal rate of rise of phase 0 (V_{max}) were displayed on Nihon Kohden VC-10 storage oscilloscope and photographed. The results before and after administration of Cim were quantified from the same cell.

Measurement of A-V conduction time New Zealand rabbits of either sex weighing 1.8 ± 0.2 kg were anesthetized with urethane 1 g · kg^{-1} iv. Lead II electrocardiogram (ECG) was recorded.

Statistics Date were analysed for statistical significance by *t* test for paired values.

Drug Cim was produced by Wujin Factory of Drug Production, Chang Zhou 213101, China, lot 890303.

RESULTS

Effects of Cim on AP of rabbit papillary muscle and SAN pacemaker cells Cim

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(0.01, 0.1, 1, and 2 mmol · L^{-1}) was added in every 20 min cumulatively. Cim (0.01 mmol · L^{-1}) prolonged the duration of 50% repolarization (APD_{50}) and of 90% repolarization (APD_{90}) of AP in papillary muscle by 7.8% and 3.8% ($P<0.05$), respectively. Cim (0.1 mmol · L^{-1}) also prolonged the duration of 20% repolarization (APD_{20}) and ERP by 18.9% and 14.2% ($P<0.05$–0.01), respectively. ERP / APD > 1. When the concentration of Cim was > 1 mmol · L^{-1}, all parameters changed significantly ($P<0.01$), including a decrease of V_{max} and of action potential amplitude (APA) by 30% and 10%, respectively (Tab 1).

The effects of Cim on SAN pacemaker cell were similar to its effects on papillary muscle. Cim (0.01 mmol · L^{-1}) prolonged APD_{50} and sinus circle length (SCL) by 7% and 4% ($P<0.05$–0.01), respectively. Cim (0.1 mmol · L^{-1}) prolonged APD_{90} by 10% ($P<0.01$). When the concentration of Cim was 1 mmol · L^{-1}, all parameters were changed significantly ($P<0.05$–0.01), including the decrease of V_{max} and of APA by 33% and 17%, respectively, and APD_{20} was prolonged by 30% (Tab 2).

Effects of Cim on A–V conduction In anesthtized rabbits, Cim 10, 50, 100, and 150 mg · kg^{-1} were injected iv every 15 min. ECG was taken at 5, 10, and 15 min.

Cim (100 mg · kg^{-1}) prolonged the P–R interval by 7% ($P<0.05$). But it did not affect the heart rate (Tab 3).

DISCUSSION

It is known that phase 0 depolarization of fast AP in myocardial cell was caused by fast inward sodium current (I_{Na})[4]. Cim induced decrease of V_{max} and APA of AP in papillary muscle may be a result of blocking sodium channel. Prolongation of ERP could explain that the recovery of sodium channel deactivation is also prolonged. The slow inward current (I_{si}) carried by either Ca^{2+} or Ca^{2+}–Na^{+} is the only component of the AP upstroke in dominant pacemaker cells of SAN and it plays an importent role in V_{max}, APA and SP_4 of AP[5,6]. The effects of Cim, decrease of V_{max}, APA and SP_4 of dominant pacemaker cells in SAN, may be resulted from depression of I_{si}. Prolongation of APD may be resulted from blockade of K^{+} channel of blockade of Ca^{2+} channel that induced decrease of outward I_K[6]. All these experimental results showed that Cim unequally blocked the sodium, calcium, and potassium channels. It suggests that Cim, like quinidine[7], possesses a membrane stabilizing effect, which may be the electrophysiological basis of Cim anti-arrhythmic effects.

McCall and Lui Proved that histamine of the heart increases verapamil-sensitive sodium influx via the mediation of H_2-receptor[8]. Muramatsu *et al* proved that histamine of the heart increases the calcium and potassium via

Tab 1. Effects of cimetidine on action potential of rabbit papillary muscle. $n=11$, $\bar{x}\pm s$. $^{*}P>0.05$, $^{**}P<0.05$, $^{***}P<0.01$ *vs* control.

Concentration / mmol · L^{-1}	V_{max} / V · s^{-1}	APA / mV	APD_{20} / ms	APD_{50} / ms	APD_{90} / ms	ERP / ms
0	134 ± 10	104 ± 6	41 ± 4	79 ± 7	127 ± 10	128 ± 8
0.01	133 ± 10*	104 ± 7*	46 ± 8*	85 ± 9***	132 ± 14***	127 ± 16*
0.1	128 ± 9*	103 ± 7*	49 ± 10***	91 ± 10***	136 ± 17***	135 ± 13**
1	117 ± 12***	101 ± 8***	64 ± 9***	117 ± 13***	169 ± 20***	167 ± 12***
2	94 ± 12***	93 ± 6***	78 ± 9***	136 ± 14***	193 ± 23***	204 ± 17***

Tab 2. Effects of cimetidine on action potential of sinoatrial node in rabbit. $n=11$, $\bar{x}\pm s$. $^{*}P>0.05$, $^{**}P<0.05$, $^{***}P<0.01$ *vs* control.

Concentration / mmol · L^{-1}	V_{max} / V · s^{-1}	APA / mV	APD_{20} / ms	APD_{50} / ms	APD_{90} / ms	SP_4 / mV · s^{-1}	SCL / ms
0	2.1 ± 0.7	70 ± 10	34 ± 2	62 ± 8	113 ± 18	61 ± 12	438 ± 84
0.01	2.2 ± 0.6*	70 ± 9*	35 ± 3*	66 ± 9***	119 ± 20*	59 ± 20*	455 ± 90**
0.1	1.9 ± 0.6*	68 ± 8*	36 ± 4*	70 ± 10***	125 ± 22**	56 ± 11***	473 ± 88**
1	1.6 ± 0.7*	63 ± 7**	41 ± 7**	86 ± 20**	163 ± 42***	55 ± 9**	496 ± 85***
2	1.4 ± 0.5***	58 ± 7***	46 ± 9***	96 ± 23***	185 ± 50***	53 ± 6***	517 ± 79***

Tab 3. Effects of cimetidine on ECG in anesthetized rabbit. $n=10$, $\bar{x}\pm s$. $^{*}P>0.05$, $^{**}P<0.05$, $^{***}P<0.01$ *vs* control.

Dose / mg · kg^{-1}	P–R interval / ms			Heart rate / bpm		
	5 min	10 min	15 min	5 min	10 min	15 min
0	58 ± 6			275 ± 29		
10	58 ± 6*	58 ± 6*	58 ± 7*	278 ± 26*	278 ± 28*	274 ± 31*
50	58 ± 6*	60 ± 6*	58 ± 6*	291 ± 25**	279 ± 22*	286 ± 41*
100	62 ± 8**	62 ± 8**	64 ± 8***	287 ± 23*	281 ± 22*	275 ± 23*
150	69 ± 10***	68 ± 10***	66 ± 10***	282 ± 27*	284 ± 26*	280 ± 28*

mediation of H_2–receptor[9]. So, the effects of Cim are achieved mainly through blocking the myocardial H_2–receptors. But direct effect of Cim on the myocardium beyond receptors can not be excluded. Meanwhile, prolongation of A–V conduction, which accords with that of Borchard *et al*[10], further confirmed that H_2–receptor of heart participates in A–V conduction besides H_1–receptor.

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西咪替丁对兔心肌的电生理作用

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提要 用电生理方法研究西咪替丁(Cim)对离体兔心乳头状肌、窦房结动作电位及麻醉兔房室传导的影响. Cim (0.01、0.1、1、2 mmol · L^{-1})浓度依赖性地延长动作电位时程(APD)和有效不应期(ERP)、减慢零相最大除极速率(V_{max})和 4 相自动除极速率(SP_4)、降低动作电位幅度(APA)、减慢房室传导. 提示 Cim 具有奎尼丁样膜稳定作用.

关键词 西咪替丁; 电生理学; 动作电位; 乳头状肌; 窦房结; 心电描记术