Tri 具有增加脑血流量的作用.

Tri 的作用机理可能是多方面的，但其钙拮抗作用及抗 5-羟色胺作用，不容忽视，因其与一般钙拮抗剂不同，在选择扩张脑血管增加流量的同时，对心输出量及心肌血流量亦均有明显增加，提示 Tri 更适合于伴有心功能不良的缺血性脑血管疾病.

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4 Toward R. The selective inhibition of serotonin-induced contraction of rabbit cerebral vascular smooth muscle by calcium-antagonistic dihydropyridines: an investigation of the mechanism of action of nimodipine. *Circ Res* 1981; **48** : 650

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Electrophysiological effects of *m*-nisoldipine and nisoldipine on papillary muscles of guinea pig

AN Rui-Hai, HE Rui-Rong (*Department of Physiology, Institute of Basic Medicine, Hebei Medical College, Shijiazhuang 050017, China*)

ABSTRACT The effects of *m*-nisoldipine (*m*-Nis) and nisoldipine (Nis) on action potentials of papillary muscles in guinea pigs were studied using intracellular microelectrodes. The results : (1) APD and V_{max_s} in normal papillary muscles were reduced by *m*-Nis and Nis. However, the APA, V_{max_f} and overshoot were not affected. (2) In the partially depolarized papillary muscles, the APA, overshoot, V_{max} and APD were depressed in a dose-dependent manner. The inhibitory effects of Nis on APA, APD_{50} and PPD were greater than those of the *m*-Nis. (3) There was a good correlation between APD_{50} and PPD derived from a linear regression. By the linear equation, PPD was easily calculated from APD_{50}.

KEY WORDS *m*-nisoldipine; nisoldipine; microelectrodes; papillary muscles; action potentials; electrophysiology

New calcium antagonist *m*-nisoldipine (*m*-Nis) reduced the ischemic arrhythmias by improving the electrical stability in conscious and anesthetized rats[1,2]. In this article, the effects of *m*-Nis and Nis on action potentials (AP) in normal and partially depolarized papillary muscles of guinea papillary were studied with intracellular microelectrodes.

MATERIALS AND METHODS

Guinea pigs weighing 0.45 ± SD 0.10 kg (both sexes) were used. The animals were stunned by heavy blow on the head. The papillary muscle was excised from the right ventricle. One end of the papillary muscle was fixed to the silicon rubber placed on the bottom of perfusing chamber by stainless steel needle. The other end was connected to the force transducer (TB-612T). The preparation was perfused with modified Krebs-Henseleit solution (K-H solution) at a flow rate of 4 ml / min for at least 30 min before experiment. The perfusate maintained

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at 35℃ was continuously equilibrated with 95% O_2+ 5% CO_2.

The papillary muscle was paced by square pulse (duration 1 ms; intensity 1.5 times threshold) provided by an electronic stimulator (SEN−3201, Nihhon Kohdan) through bipolar stainless steel electrodes. The glass microelectrode was inserted into the papillary muscle to record the electrical signal intracellularly. The signal after amplifier (MEZ−8201) was fed to a polypraph (RM−6000) and monitored with an oscilloscope. The amplified signal was analyzed by microcomputer (Apple−Ⅱ).

Resting potential (RP), amplitude of action potential (APA), overshoot (OS), and durations of 90% and 50% repolarization (APD_{90} and APD_{50}) were displayed in digit by the microcomputer. The rate of depolarization was divided into 2 parts—the fast and slow components (V_{maxf} and V_{maxs})[3] by the microcomputer using a program designed by our department[4]. V_{maxf} and V_{maxs} were used to reflect the properties of Na^+ and Ca^{2+} currents respectively. The duration of plateau phase (PPD) was defined by the microcomputer through linear regression. Parameters of AP were stored into diskette.

The papillary muscle was gradually depolarized to −50 mV by K−H solution containing KCl 18 mmol / L. While the muscle was being depolarized, the AP could not be induced even with more intense stimuli. However, slow response AP was induced by electrical stimulation so long as isoprenaline (1.5 μmol / L) was added to the perfusate.

The protocol includes 2 parts of experiments : (1) Effects of *m*−Nis on the AP of normal papillary muscles. The animals were divided into 3 groups with 10 in each: control, nisoldipine (Nis) 0.2 μmol / L, and *m*−Nis 0.2 μmol / L. (2). Effects of *m*−Nis on the action potentials of partially depolarized papillary muscles. The animals were divided into 7 groups: control, Nis 0.2 μmol / L, and the other 5 groups were given *m*−Nis 0.002 − 20 μmol / L.

After recording 3 control AP, the preparation was perfused with K−H solution containing *m*−Nis or Nis. The solvent and resource of *m*−Nis and Nis were described earlier[1]. The time required to change the perfusate was within 1 min. The AP were recorded 5, 10 and 20 min after medication. The preparation was washed with K−H solution to observe the recovery of AP.

The changes of parameters of AP expressed as mean ± SD were analyzed using t test (one way). Differences among groups were tested using F test.

RESULTS

Effects of *m*−Nis on AP in normal papillary muscles After 5 min of perfusion with K−H solution containing *m*−Nis 0.2 μmol / L, the duration of AP (APD) and V_{maxs} began to diminish. 10 min later, the APD was greatly reduced. While a steady state reached after 20 min of perfusion, the reduction of 20% for APD_{90}, 35% for PPD, and 30% for V_{maxs} were seen. The parameters of AP were partially recovered after 30 min of washing. But a difference still existed as compared with the control group ($P<0.01$) at the end of washing. There was no significant difference between the effects of Nis and *m*−Nis at equal dose. Both *m*−Nis and Nis had no effect on APA, OS, V_{maxf} and RP (Tab 1).

Effects of *m*−Nis on AP in partially depolarized papillary muscles

1 Comparison of the effects of *m*−Nis and Nis In the partially depolarized papillary muscles, RP was −51 ± 4 mV. The amplitude of slow response AP was 88 ± 5 mV, V_{max} was 27 ± 4 V / s. APD was reduced by *m*−Nis at 0.2 μmol / L. APD_{90} and PPD were shortened by 27% and 32% respectively. APA, OS and V_{max} were also reduced ($P<0.01$).

Tab 1. Effects of *m*-nisoldipine 0.2 μmol / L and nisoldipine 0.2 μmol / L on action potentials of guinea pig papillary muscles. $n=10$, $\bar{x}$ ± SD. $^{*}P>0.05$, $^{**}P<0.05$, $^{***}P<0.01$ *vs* solvent control; $^{+}P>0.05$, $^{++}P<0.05$, $^{+++}P<0.01$ *vs* *m*-nisoldipine.

Parameters	Solvent control		*m*-Nisoldipine		Nisoldipine	
	Normal K^+	High K^+	Normal K^+	High K^+	Normal K^+	High K^+
RP (mV)	−73 ± 4	−51 ± 4	−73 ± 3*	−48 ± 5*	−71 ± 4* +	−51 ± 5* +
OS (mV)	35 ± 4	37 ± 4	33 ± 4*	32 ± 6**	32 ± 4* +	30 ± 7** +
APA (mV)	107 ± 5	88 ± 5	106 ± 4*	79 ± 6***	104 ± 7* +	73 ± 6*** ++
V_{maxf}(V / s)	222 ± 33		238 ± 58*		219 ± 30* +	
V_{maxs}(V / s)	13 ± 2	27 ± 4	10 ± 1***	20 ± 4***	9 ± 2*** +	18 ± 5*** +
APD_{90} (ms)	139 ± 10	154 ± 12	102 ± 11***	112 ± 27***	109 ± 18*** +	112 ± 13*** +
APD_{50} (ms)	118 ± 7	138 ± 11	79 ± 11***	79 ± 22***	83 ± 16*** +	87 ± 12*** ++
PPD (ms)	98 ± 7	106 ± 9	60 ± 12***	73 ± 18***	63 ± 14*** ++	63 ± 14 *** +++

RP: resting potential; OS: overshoot;APA: amplitude of action potential; V_{maxf} : fast component of maximal depolarizing rate; V_{maxs} : slow component of maximal depolarizing rate; APD_{90}: duration of 90% repolaziration; APD_{50}: duration of 50% repolaziration; PPD: duration of plateau phase; High K^+ = KCl 18 mmol / L.

Tab 2. Dose-response relationship of *m*-nisodipine on action potentials of guinea pig papillary muscles in K-H solution containing KCl 18 mmol / L. $n=10$, $\bar{x}$ ± SD. $^{*}P>0.05$, $^{**}P<0.05$, $^{***}P<0.01$ *vs* solvent control.

Parameter	Control	*m*-Nisoldipine(μmol / L)				
		0.002	0.02	0.2	2	20
RP (−mV)	−51 ± 3	−50 ± 4*	−48 ± 5*	−51 ± 5*	−50 ± 3*	−47 ± 7*
OS (mV)	35 ± 6	35 ± 6*	35 ± 5*	30 ± 3*	28 ± 12*	26 ± 9*
APA (mV)	86 ± 7	86 ± 7*	83 ± 6*	77 ± 6**	78 ± 10*	75 ± 11*
V_{maxs}(V / s)	28 ± 6	27 ± 8*	26 ± 3*	21 ± 4**	16 ± 2***	14 ± 3***
APD_{90} (ms)	149 ± 12	140 ± 21*	127 ± 20***	108 ± 20***	109 ± 12***	97 ± 19***
APD_{50} (ms)	136 ± 11	134 ± 10*	103 ± 41***	96 ± 21***	92 ± 13***	85 ± 22***
PPD (ms)	107 ± 11	101 ± 10*	81 ± 31***	73 ± 18***	66 ± 13***	59 ± 19 ***

The actions of Nis on APA, APD_{50} and PPD were more potent as compared with those of *m*-Nis (Tab 1).

2 The dose-response relationship of *m*-Nis The parameters of AP were not affected by *m*-Nis 2 nmol / L. APD was shortened by *m*-Nis 20 nmol / L with a reduction of 15% for APD_{90} and 24% for PPD. However, the V_{max} showed no change at this concentration. The APD was progressively reduced as the concentration of *m*-Nis was increased to 0.2, 2 and 20 μmol / L. APA and V_{max} were also significantly depressed (Tab 2). In 3 preparations, the slow response AP could not be evoked at 20 μmol / L.

The inhibitory effect of *m*-Nis on slow response AP was more prominent as the concentration of *m*-Nis increased. The APD and APA were gradually reduced (Fig 1).

Correlation analysis of APD_{50} with PPD PPD measured through linear regression was 25 ms shorter than APD_{50}. the

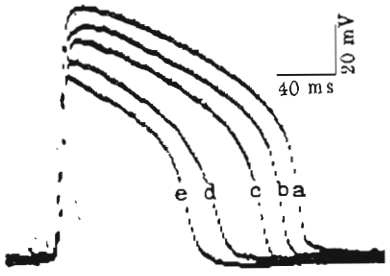

Fig 1 Effects of *m*-nisoldipine on action potentials of guinea pig papillary muscles in K-H solution containing KCl 18 mmol / L. a) control, b) 20 nmol / L, c) 0.2 μmol / L, d) 2 μmol / L, e) 20 μmol / L

correlation analysis revealed that there was good correlation between APD_{50} and PPD ($r = 0.985$, $P < 0.01$). The linear equation between them was as follows:

$$\hat{Y} = 0.83\,X - 9.79$$

$\hat{Y}$ = PPD, X = APD_{50}

DISCUSSION

This is the first report on the electrophysiological effects of *m*-Nis and Nis. In normal guinea pig papillary muscles, APD and V_{maxs} were significantly reduced by *m*-Nis and Nis. But RP, APA, OS and V_{maxf} were not affected. The results indicate that *m*-Nis and Nis has little effect on the depolarisation phase of the fast response AP, because *m*-Nis and Nis selectively act on voltage-dependent Ca^{2+} channel[5]. The accelerated repolarization could be attributed to the reduction of Ca^{2+} influx in plateau phase.

In the high K^+ depolarized papillary muscle, the fast response AP was completely inhibited. Slow response AP with low amplitude and low rate of depolarization is suitable to be used for studying the electrophysiological effects of calcium antagonists[6]. The parameters of depolarization were greatly depressed by *m*-Nis and Nis. The depolarizing process supperimposed on the basis of partial depolarization is mainly dependent on the Ca^{2+} influx. So the calcium antagonists could depress the depolarization. The inhibitory effect of *m*-Nis on slow response potential might be an important characteristic for its anti-arrhythmic effect[7,8].

The curves of dose-response relationship of the inhibitory effect of *m*-Nis on APD_{50} and V_{max} were not parallel. This indicates that the sensitivity of APD_{50} to *m*-Nis is not the same as that of V_{max}. The limited reduction of APD is probably related to the plateau phase which is influenced by both Ca^{2+} influx and K^+ outflow. So, only a limited change could be observed by blocking Ca^{2+} channel. However, the V_{max} of slow response AP is almost completely dependent on the Ca^{2+} influx.

APD_{50} is often used to reflect the change in PPD[9,10]. However, APD_{50} is susceptible to the changes in the duration of phase 1 and the slope of phase 3, and therefore it is not an exact measurement for plateau phase. The results measured with the microcomputer showed that PPD was about 25 ms shorter than APD_{50}, and there was a good correlation between the two parameters. PPD calculated from the equation provided in the article was very consistent with that which was directly measured by the microcomputer.

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间尼索地平和尼索地平对豚鼠乳头状肌的电生理效应

安瑞海、何瑞荣 (河北医学院基础医学研究所生理室, 石家庄 050017, 中国)

提要 利用细胞内微电极技术, 观察间尼索地平(*m*–Nis)和尼索地平(Nis)对豚鼠乳头状肌动作电位的影响, 结果:*m*–Nis 和 Nis 可明显缩短正常乳头状肌动作电位时程, 抑制 V_{maxs}, 而对 RP, APA, OS 和 V_{maxf} 无影响; 对部分去极化的乳头状肌, *m*–Nis 和 Nis 能显著抑制动作电位的幅值、超射和 V_{max}, 缩短动作电位时程, 此抑制作用有剂量依赖性, Nis 的作用明显强于 *m*–Nis; 线性回归法测算的 PPD 与 APD_{50} 之间有良好的相关性, 根据所求得的方程, 即可方便地从 APD_{50} 计算 PPD.

关键词 间尼索地平; 尼索地平; 微电极; 乳头状肌; 动作电位; 电生理学

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苄基四氢巴马汀对心肌动作电位及浦氏纤维跨膜钾、钙离子流的影响[1]

曾维忠、夏国瑾、姚伟星、宗贤刚、江明性 (同济医科大学药理教研室, 汉口 430030, 中国)

Effects of benzyltetrahydropalmatine on action potentials of myocardium and transmembrane K^+ and Ca^{2+} currents in Purkinje fibers

ZENG Wei–Zhong, XIA Guo–Jin, YAO Wei–Xing, ZONG Xian–Gang, JIANG Ming–Xing
(*Department of Pharmacology, Tongji Medical University, Hankou 430030, China*)

ABSTRACT Standard microelectrode and two–microelectrode voltage clamp techniques were used to study the effects of benzyltetrahydropalmatine (BTHP) on action potentials of isolated myocardium and transmembrane K^+ and Ca^{2+} currents in Purkinje fibers. The effect of BTHP 3–100 μmol / L consisted of prolongation of the action potential duration and reduction of delayed rectifier current (I_k) in concentration–dependent manner. At concentration above 200 μmol / L, the contractile force of the isolated myocardium was depressed and in voltage clamp experiments the slow inward current (I_{si}) was reduced. These results suggest that the inhibition of I_k induced by BTHP was in relation to its anti–arrhythmic action.

KEY WORDS berbines; benzyltetrahydropalmatine; myocardium; Purkinje fibers; action potentials; electrophysiology; myocardial contraction

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提要 应用细胞内标准微电极方法及双微电极电压钳技术研究苄基四氢巴马汀(BTHP)对心肌细胞动作电位及浦氏纤维跨膜离子流的影响. 结果表明 BTHP 依浓度地延长豚鼠心肌细胞动作电位时程、阻滞羊浦氏纤维延迟整流电流, 大剂量 BTHP 可抑制豚鼠心肌收缩力、阻滞犬浦氏纤维慢内向电流. 提示 BTHP 阻滞钾通道是其抗心律失常的重要机理.

关键词 小檗因类; 苄基四氢巴马汀; 心肌; 浦氏纤维; 动作电位; 电生理学; 心肌收缩

苄基四氢巴马汀(benzyltetrahydropalmatine, BTHP)是巴马汀的衍生物, 具有抗多种实验性心律失常作用[1]. 本文应用细胞内标准微电极方法及双微电极电压钳技术研究 BTHP 对于心肌细胞动作电位及浦氏纤维跨