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Cardiac electric activity of 1-{2-[(6-methoxyl)-naphthylmethyl]}-1-methyl-*N*-piperidinylacethyl -6,7- dimethoxyl -1,2,3,4- tetrahydroisoquinoline in SHR and WKY rats

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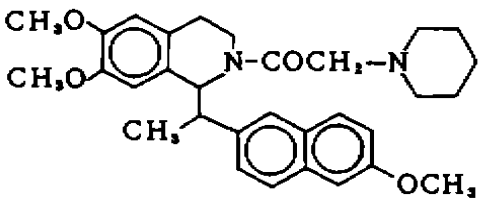
ABSTRACT 1-{2-[(6-Methoxyl)-naphthylmethyl)]}-1-methyl-*N*-piperidinylacethyl-6,7-dimethoxyl-1,2,3,4-tetrahydroisoquinoline (CPU-23), a substituted tetrahydroisoquinoline, reduced the voltages of P wave and J point, prolonged PR interval, and slowed sinus rhythm of ECG in spontaneously hypertensive rats (SHR) and agematched normotensive WKY rats. The effects of CPU-23 on cardiac electric activity were stronger in SHR than in WKY rats ($P<0.05$ or $P<0.01$). The results suggest that CPU-23 have a calcium antagonistic activity on rat hearts and that calcium antagonists may exert a stronger inhibition of the cardiac electric activity in hypertensive rats than in normotensive rats.

KEY WORDS CPU-23; isoquinolines; electrocardiography; inbred SHR rats; inbred WKY rats

In a previous study, with a [^{3}H]nitrendipine binding assay, we screened a series of substituted tetrahydroisoquinolines in order to develop calcium antagonists based on the lead compounds isolated from Chinese medicinal herbs[1]. One of the most potent compounds identified in this series to inhibit [^{3}H]nitrendipine binding to rat cerebral cortical membranes was 1-{2[(6-methoxyl)-naphthylmethyl]}-1-methyl-*N*-piperidinylacethyl-6,7-dimethoxyl-1,2,3,4-tetrahydroisoquinoline (CPU-23), which also inhibited high KCl-induced contraction of rat aorta *in vitro* and produced hypotension and bradycardia *in vivo*, suggesting that it was a putative calcium antagonist[1,2].

In the present study, we further investigate its effects on cardiac electric activity of rats. Since calcium antagonists have been reported to exert a stronger inhibition of the noradrenaline-induced contraction of rat arterial muscle in essential hypertensive human and spontaneously hypertensive rats (SHR) than in normotensive human and rats[3], we have also compared the cardiac electric activity of CPU-23 between SHR and age-matched normotensive WKY rats to investigate whether there is a significant difference between its effects in SHR and WKY rats.



CPU-23

MATERIALS AND METHODS

Male SHR (6 months, 320±*s* 15 g) and age-matched normotensive WKY rats were anesthetized with pentobarbitone (75 mg·kg^{-1}, ip). Tracheotomy and cannulation of right femoral vein were made. The limb II lead of electrocardiogram (ECG) was monitored continuously on an oscilloscope (Gould, Type 1425) and recorded by an electrocardiograph (Fukuda, model 501D). After ECG had stabilized, generally 10 min after surgical operations, it was recorded as control, and then the effects of CPU-23 iv were monitored over the next hour. The rectal temperature was maintained at 37℃ with a table lamp.

CPU-23·HCl, synthesized by Professor PENG Si-Xun of China Pharmaceutical University[4], was dis-

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solved in saline before used.

Data were expressed as $\bar{x} \pm s$ and compared by paired t test.

RESULTS

Effects on ECG in SHR and WKY rats CPU-23 (3—10 mg·kg^{-1}, iv) immediately reduced, even inverted P wave of ECG in SHR and WKY rats. It also reduced J point (representing ST segment in rats) in a dose-dependent manner. The effects induced by CPU-23 3 mg·kg^{-1}, but not 10 mg·kg^{-1} vanished in 1 h. However, even CPU-23 10 mg·kg^{-1} did not affect significantly the voltages of R and T waves in SHR and WKY rats. CPU-23 3 mg·kg^{-1} prolonged PR interval and slowed sinus rhythm of SHR and WKY rats, but did not affect QRS complex. Intermittent iv of increasing doses of CPU-23 prolongated PR interval and slowed sinus rhythm of rat hearts in a dose-dependent manner, but did not affect significantly QRS complex (Tab 1). The effects of CPU-23 lasted more than 1 h.

Comparison of ECG changes in SHR and WKY rats Before the iv of CPU-23, there was no significant difference in the voltages of various waves of ECG between SHR and WKY rats. After CPU-23, the effects on P wave and J point were stronger in SHR than in WKY rats. The prolongation of PR interval and slowing sinus rhythm were more pronounced in SHR than in WKY rats (Tab 2).

Tab 2. ECG changes after iv CPU-23 10 mg·kg^{-1} in SHR and WKY rats. $n=5$, $\bar{x} \pm s$.
$^{b}P<0.05$, $^{c}P<0.01$ vs SHR rats.

	SHR	WKY
P wave/mV	0.16±0.06	0.09±0.02[b]
J point/mV	0.40±0.07	0.15±0.06[c]
PP interval/ms	0.38±0.09	0.19±0.06[c]
PR interval/ms	0.06±0.02	0.02±0.01[b]

DISCUSSION

The present results are consistent with the observations by Fleckenstein[5] from simple ECG recordings on anesthetized guinea pigs that intravenous infusion of verapamil, D600, nifedipine typically slows Ca-dependent sinus discharge rate and AV conduction as reflected by the frequency of P wave and the duration of PR interval but does not alter Na-dependent intraventricular impulse propagation as reflected by the duration of QRS, suggesting that CPU-23 exert a calcium antagonistic activity

Tab 1. Effects of intermittent iv injections of increasing doses of CPU-23 on ECG in SHR and WKY rats. $n=5$, $\bar{x} \pm s$. $^{b}P<0.05$, $^{c}P<0.01$ vs control. (Negative sign represents the upended waves).

	Inbred spontaneously hypertensive rats			Inbred Wistar Kyoto rats		
	Control	3 mg·kg^{-1}	10 mg·kg^{-1}	Control	3 mg·kg^{-1}	10 mg·kg^{-1}
P wave/mV	0.10±0.01	−0.05±0.02[b]	−0.04±0.01[b]	0.07±0.01	0.06±0.02	0.01±0.00
PR interval/ms	0.04±0.01	0.06±0.01[b]	0.11±0.02[c]	0.04±0.01	0.06±0.01	0.07±0.01[b]
QRS complex/ms	0.02±0.00	0.02±0.00	0.02±0.01	0.03±0.01	0.02±0.01	0.02±0.00
R wave/mV	0.60±0.03	0.49±0.03	0.43±0.07	0.79±0.02	0.75±0.03	0.61±0.09
J point/mV	−0.02±0.01	−0.16±0.06[b]	−0.40±0.04[c]	−0.02±0.01	−0.05±0.02	−0.18±0.02[c]
T wave/mV	0.16±0.01	0.16±0.01	0.18±0.02	0.10±0.01	0.08±0.01	0.10±0.03

on rat hearts in intact animals. However, the exact therapeutic significance of CPU-23 reducing J point is obscure now.

The inhibitory effects of calcium antagonists on tension development in arterial strips were greater in SHR than WKY rats[3], suggesting that abnormalities of Ca^{2+} channels in the cell membrane of arterial smooth muscle might exist in the SHR[6,7]. Our findings suggest that calcium antagonists may also exert a stronger inhibtion of the cardiac electric activity in hypertensive rats than in normotensive rats. Serveral properties of the myocardial cell membrane are altered in SHR including Ca^{2+}-binding and uptake of sarcoplasmic reticulum[8] as well as of the sarcolemma[9] and the changes in SHR might reflect a functional adaptation[10]. This may explain why the inhibitory effects of calcium antagonists on the cardiac electric activity were greater in SHR than in WKY rats. However, further experiments will provide an answer to the precise mechanism of this action.

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1-{2-[(6-甲氧基)-甲萘基]}-1-甲基-*N*-乙酰六氢吡啶-6,7-二甲氧基-1,2,3,4-四氢异喹啉对SHR和WKY大鼠心电的作用

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摘要 四氢异喹啉新化合物CPU-23降低SHR和同龄WKY大鼠心电图的P波和J点电压, 延长PR间期并减慢其窦性心率. CPU-23的上述作用在SHR比在WKY大鼠强($P<0.05$或$P<0.01$). 本结果提示, CPU-23在整体动物水平具有钙拮抗作用, 而钙拮抗剂对高血压大鼠心脏电活动的抑制作用可能比对正常大鼠要强.

关键词 CPU-23; 异喹啉类; 心电描记术; 近交SHR大鼠; 近交WKY大鼠