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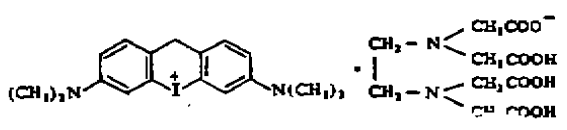
# Effects of 3,6-dimethylamino-dibenzopyriodonium edetate on action potentials in guinea pig papillary muscles

JI Guang-Ju[1], ZHAO De-Hua, LIU De-Qiang, SHENG Bao-Heng
(*Department of Pharmacology, Fourth Military Medical University, Xi-an 710032, China*)

**ABSTRACT** The effects of 3,6-dimethylamino-dibenzopyriodonium edetate (IHC-72) on action potentials (AP) and slow response action potentials of guinea pig papillary muscles were studied with intracellular microelectrodes. IHC-72 12.7, 25.4, and 50.8 μmol·$L^{-1}$ decreased the maximal upstroke velocity ($V_{max}$), amplitude of action potential (APA), over shot (OS), and resting potential (RP) while prolonged the action potential duration at 30%, 50%, 90%, and 100% repolarization ($APD_{30}$, $APD_{50}$, $APD_{90}$, and $APD_{100}$). IHC-72 25.4 and 50.8 μmol·$L^{-1}$ decreased the APA, $V_{max}$, and prolonged $APD_{50}$ and $APD_{90}$ under high $K^+$ superfusion. IHC-72 25.4 and 50.8 μmol·$L^{-1}$ depressed the automaticity, APA, and maximal diastolic potential (MDP) of the slow response action potentials induced by $BaCl_2$. The results indicated that IHC-72 might nonspecifically inhibit the transmembrane movement of $Ca^{2+}$, $Na^+$, and $K^+$.

**KEY WORDS** 3,6-dimethylamino-dibenzopyriodonium; papillary muscles; action potentials

3,6-Dimethylamino-dibenzopyridodonium edetate (IHC-72) has anti-arrhythmic action in animal models[1]. The anti-arrhythmic action of IHC-72 is similar to that of verapamil[2]. Our previous experiment *in vitro* suggested that the antiarrhythmic action of IHC-72 was possiblly related to the inhibition of calcium current in myocardial cells[3]. In the present study, we observed the effects of IHC-72 on the action potentials and slow response action potentials using microelectrode in guinea pig papillary muscles.



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[1] Now in *Department of Pharmacology, Medical College of General Logistics Department PLA, Beijing 100071, China.*

## MATERIALS AND METHODS

**Drugs** IHC-72, synthesized and supplied by Prof CHEN Shu-Ying (*Department of Chemistry, Lanzhou University*), was dissolved in distilled water, the highest concentration in bath being 0.2%. Lidocaine (Lid, *Tianjing People Pharmaceutic Factory, Tianjing*); verapamil (Ver, *Beijing Pharmaceutic Factory, Beijing*).

**Experimental procedure** Forty guinea pigs of either sex, weighing 393± s 31 g, were supplied by Experimental Animal Center of Fourth Military Medical University. The preparations of papillary muscles were perfused with Tyrode solution (5 ml·$min^{-1}$) aerated with 95% $O_2$+5% $CO_2$ at 35± 0.5℃ and pH 7.35± 0.5. The preparations were electrically driven with pulses of 3-ms duration and 1.5 times threshold voltage at 1 Hz frequency delivered from the stimulator (XF-3 physiological electronic stimulator, Shanghai). Transmembrane action potentials were recorded[4], and the parameters were measured and photoed with a camera (SB 40813, Japan). Each preparation was stabilized for at least 40 min before experiment. Only one drug was allowed to be used for one preparation. When the impalement remained stable and drug effects disappeared completely, a second drug concentration was superfused onto the same preparation in some experiments. This allowed to compare the effects of different drug concentrations.

For slow responses, the concentration of KCl in Tyrode solution was elevated to 25 mmol·$L^{-1}$, and that of NaCl was lowered to 125 mmol·$L^{-1}$ from 135 mmol·$L^{-1}$ to keep the osmotic pressure of the solution unchanged.

**Statistical analysis** Data were expressed as

$\bar{x}\pm s$, compared with the paired $t$ test.

## RESULTS

**Effects of IHC-72 and lidocaine on fast response action potentials** After superfusing with Tyrode solution containing IHC-72 12.7, 25.4, and 50.8 $\mu$mol·L$^{-1}$ for 15-20 min, OS, APA, RP, and $V_{max}$ were decreased, while $APD_{50}$, $APD_{90}$, and $APD_{100}$ were prolonged. IHC-72 50.8 $\mu$mol·L$^{-1}$ also prolonged the $APD_{30}$ (Tab 1). Lidocaine 55 $\mu$mol·L$^{-1}$ decreased the OS, APA, and RP from 28± 2, 117± 6, and 87± 4 mV to 26± 3, 112± 6, and 84± 4 mV ($P<0.05$, $<0.01$, and $<0.01$), respectively. But the $APD_{30}$, $APD_{50}$, and $APD_{90}$ were shortened from 105± 11, 146± 5, and 190± 6 ms to 100± 11, 139± 6, and 180± 6 ms ($P<0.05$, $P<0.05$, and $P<0.01$), respectively, in contrary to the prolongation in the IHC-72 group.

**Effects of IHC-72 and Ver on slow response action potentials** After $Na^+$ channels were inactivated by KCl 25 mmol·L$^{-1}$, isoproterenol 1 $\mu$mol·L$^{-1}$ for 20 min, and stimulation of 0.25 Hz in an 8-ms duration and an intensity of twice the threshold voltage, a typical slow response action potential was recorded[15]. Then the preparations were superfused by Tyrode solution containing IHC-72 25.4 and 50.8 $\mu$mol·L$^{-1}$ or Ver 0.45 $\mu$mol·L$^{-1}$ for 15-20 min. Results (Tab 2) indicated that IHC-72 decreased the APA and $V_{max}$, while prolonged the $APD_{50}$ and $APD_{90}$ of the slow response action potentials. Ver had the same effects on the APA and $V_{max}$ as IHC-72 did, but shortened the $APD_{50}$ and $APD_{90}$.

**Effects of IHC-72 and Lid on $BaCl_2$-induced arrhythmia** IHC-72 and Lid decreased the autorhythmicity induced by $BaCl_2$. IHC-72 also decreased the APA and MDP (Tab 3).

**Tab 1. Effects of IHC-72 on action potentials in guinea pig papillary muscles.** $n=7$. $\bar{x}\pm s$. $^*P>0.05$, $^{**}P<0.05$, $^{***}P<0.01$ *vs* control.

| | Control | IHC-72 / $\mu$mol·L$^{-1}$ 12.7 | 25.4 | 50.8 |
|---|---|---|---|---|
| OS / mV | 28± 2 | 24± 1*** | 21± 2*** | 18± 2*** |
| APA / mV | 121± 5 | 115± 7*** | 106± 8*** | 97± 12*** |
| RP / mV | 92± 5 | 88± 5*** | 84± 8*** | 80± 8*** |
| $V_{max}$ / V·s$^{-1}$ | 267± 9 | 249± 11** | 237± 21** | 225± 21*** |
| $APD_{30}$ / ms | 99± 11 | 105± 4* | 117± 11* | 122± 14** |
| $APD_{50}$ / ms | 143± 11 | 164± 17** | 177± 14*** | 189± 22*** |
| $APD_{90}$ / ms | 195± 13 | 217± 31** | 235± 32*** | 249± 36*** |
| $APD_{100}$ / ms | 229± 25 | 244± 35** | 267± 42** | 285± 49*** |

**Tab 2. Effects of IHC-72 and Ver on slow action potentials induced by KCl 25 mmol·L$^{-1}$ Tyrode solution in guinea pig papillary muscles.** $n=7$. $\bar{x}\pm s$. $^*P>0.05$, $^{**}P<0.05$, $^{***}P<0.01$ *vs* control.

| | $\mu$mol·L$^{-1}$ | APA / mV | $V_{max}$ / V·s$^{-1}$ | $APD_{50}$ / ms | $APD_{90}$ / ms |
|---|---|---|---|---|---|
| Control | | 76± 5 | 12± 3 | 83± 14 | 123± 11 |
| IHC-72 | 25.4 | 74± 6** | 9± 2*** | 82± 8* | 138± 13** |
| IHC-72 | 50.8 | 67± 6** | 7± 2*** | 102± 26** | 148± 11*** |
| Control | | 76± 8 | 11± 1 | 83± 4 | 125± 13 |
| Verapamil | 0.45 | 72± 8*** | 10± 1** | 80± 4** | 116± 7** |

**Tab 3. Effects of IHC−72 and Lid on action potentials and $BaCl_2$−induced arrhythmia in guinea pig papillary muscles.** $n$= 6. $\bar{x} \pm s$. $^{*}P> 0.05$, $^{**}P< 0.05$, $^{***}P< 0.01$ *vs* control.

| | $\mu g \cdot ml^{-1}$ | APA/mV | MDP/−mV | Rate/bpm |
|---|---|---|---|---|
| Control | | 69± 3 | 53± 4 | 110± 11 |
| IHC−72 | 25.4 | 65± 1*** | 52± 4* | 98± 6*** |
| IHC−72 | 50.8 | 59± 2*** | 46± 5*** | 85± 7*** |
| Control | | 68± 8 | 49± 4 | 104± 12 |
| Lidocaine | 55 | 66± 4* | 46± 5* | 88± 7*** |

## DISCUSSION

It has been reported that IHC−65, a homologue of IHC−72, inhibited the contractility of guinea pig papillary muscles dose−dependently, shortened the APA of fast action potentials, and decreased the $V_{max}$ of slow response action potentials induced by high $K^+$ [6,7], and TAN Dun−Xian *et al*[8] thought that it was a new calcium channel blocker. In the present study, we found that IHC−72 decreased the APA and $V_{max}$, while prolonged the APD of the fast response action potentials, which suggested that it had an inhibitory effect on the inward calcium and sodium current in myocardium.

The APA and $V_{max}$ of slow response action potentials induced by high $K^+$ were thought to be mediated by the slow calcium inward current[9,10]. Some calcium antagonists, such as verapamil, could inhibit this slow response action potential induced by high $K^+$ [9]. Our experiment showed that both IHC−72 and Verapamil decreased the APA and $V_{max}$ of the slow response action potentials induced by high $K^+$ (25 mmol· $L^{-1}$). The difference between IHC−72 and verapamil was that the former prolonged APD while the latter shortened it. This phenomenon indicated that IHC−72 not only ihibited the inward calcium current but also inhibited the outward potassium current to some extent in the myocytes. The depressing effect of IHC−72 on the abnormal automaticity, APA and MDP of the slow response action potentials induced by $BaCl_2$, similar to that of IHC−65, further implied that it might inhibit the calcium current, which was consistent with the finding of our previous experiment *in vitro*[3].

Our experimental results suggested that IHC−72 inhibits $Ca^{2+}$, $Na^+$, and $K^+$ transmembrane movement in the myocytes. But it was difficult to determine which ion of IHC−72 has relatively more selectivity under such experimental conditions.

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## 3,6-(二甲氨基)-二苯骈碘杂六环依地酸盐对豚鼠乳头状肌动作电位的影响

R965.2

姬广聚[1]，赵德化，刘德强，盛宝恒
(第四军医大学药理教研室，西安 710032，中国)

**摘要** IHC-72 12.7、25.4 和 50.8 μmol·L$^{-1}$ 显著降低动作电位的 APA，OS，RP 和 $V_{max}$，延长 APD；25.4 和 50.8 μmol·L$^{-1}$ 使高 K$^+$除极慢反应动作电位的 APA 由 76± 5 mV 分别降低至 74± 6 和 67± 6 mV ($P$ 均<0.05)，$V_{max}$ 由 12± 3 V·s$^{-1}$ 分别降至 9± 2 和 7± 2 V·s$^{-1}$ ($P$ 均<0.01)，并且明显延长 APD；IHC-72 25.4 和 50.8 μmol·L$^{-1}$ 还抑制 $BaCl_2$ 诱发异常节律的 APA 和 MDP. 结果提示，IHC-72 抑制 $Ca^{2+}$，$Na^+$和 $K^+$的跨膜转运.

IHC-72

**关键词** 3,6-(二甲氨基)-二苯骈碘杂六环；乳头状肌；动作电位

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# Selective vasodilatory effect of dipfluzine on vertebral artery in anesthetized dogs

WANG Yong-Li, HE Rui-Rong[1] (*Department of Pharmacology and [1]Department of Physiology, Hebei Medical College, Shijiazhuang 050017, China*)

**ABSTRACT** Dipfluzine (Dip) is a novel calcium antagonist first developed by Department of Chemistry, Beijing University. The effects of Dip on hemodynamics and vascular resistance in vertebral (VVR), coronary (CVR), and femoral (FVR) arteries were compared with those of cinnarizine (Cin) in anesthetized dogs. Dip iv decreased dose-dependently VVR at 0.1, 0.3, 1, and 3 mg·kg$^{-1}$, CVR at 3 mg·kg$^{-1}$, and FVR at 1 and 3 mg·kg$^{-1}$. The fall of VVR by Dip iv was more remarkable than that by Cin at the matching doses. The systolic, diastolic, and mean blood pressure and total peripheral resistance were temporarily reduced equally by both of them at 1 mg·kg$^{-1}$ iv; while Dip and Cin produced no obvious changes in heart rate, cardiac index, stroke index, LVP, and $dP/dt_{max}$ at all doses. These results suggested that Dip possessed a high selectivity at different sites of the vasculature and was a more potent selective cerebral vasodilator than Cin.

**KEY WORDS** dipfluzine; cinnarizine; vascular resistance; hemodynamics; vertebral artery; coronary vessels; femoral artery; calcium channel blockers

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Our previous study using isolated blood vessels *in vitro* demonstrated that dipfluzine (Dip), a novel diphenylpiperazine calcium antagonist first developed by Department of Chemistry, Beijing University, China, was a more selective and more potent vasodilator on cerebral vessels than cinnarizine (Cin)[1]. But it remained uncertain whether these properties of Dip existed *in vivo*. The present study was to examine the selectivities of Dip and Cin on vascular resistance in various sites of the vasculature in anesthetized dogs, and to examine the peripheral hemodynamics in doses reducing the vascular resistance in cerebral arteries.

## MATERIALS AND METHODS

**Chemicals** Dip and Cin (purities of both >99.85%), synthesized by Department of Chemistry, Beijing University, were dissolved in 2% tartaric acid solution containing 20% dimethylacetamide (solvent). Drugs were injectd into femoral vein in a volume of 0.1 ml·kg$^{-1}$. Same volume of the solvent was used as control.

**Vascular resistance** Twelve mongrel dogs of