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Effects of cycloprotobuxine-A on atrial fibrillation

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KEY WORDS cycloprotobuxine-A; amiodarone; atrial fibrillation; action potentials; heart atrium

AIM: To study the effects of cycloprotobuxine-A (Cyc-A) on atrial fibrillation. **METHODS:** Atrial fibrillations *in vivo* and *in vitro* were induced by arrhythmogenic drugs. Action potentials were measured by the standard microelectrode technique. **RESULTS:** Cyc-A, similar to or slightly stronger than amiodarone (Ami), decreased incidences of atrial fibrillation elicited by $CaCl_2$-acetylcholine in mice and increased doses of aconitine, ouabain, or adrenaline to elicit atrial fibrillation in isolated guinea pig atria. Cyc-A 0.3 - 100 $\mu mol \cdot L^{-1}$ decreased the normal automaticity and 0.3 - 30 $\mu mol \cdot L^{-1}$ attenuated or almost abolished the isoprenaline-induced abnormal increase in automaticity in sinus nodal cells. In isolated left atria, Cyc-A 0.3 - 30 $\mu mol \cdot L^{-1}$ inhibited the abnormal rhythmic activity elicited by adrenaline, prolonged action potential duration (APD) and effective refractory period, and reduced excitability. At 3 - 30 $\mu mol \cdot L^{-1}$, Cyc-A also decreased the maximal velocity of depolarization (V_{max}). Cyc-A antagonized the acetylcholine-induced shortening of APD. These electrophysiologic effects were similar to those of amiodarone, but Ami did not affect the V_{max}. **CONCLUSION:** Cyc-A produces a protective effect against experimental atrial fibrillation via a prolongation of repolarization, a decease of automaticity, and an inhibition of excitability.

Both cycloprotobuxine-A (Cyc-A) and cyclovirobuxine-D are alkaloids extracted from the *Buxus*. Cyclovirobuxine-D exerted an anti-arrhythmic effect, an enhancement of myocardial force, and a protective action against myocardial ischemia in animals and human[1-3]. Cyc-A displayed a more potent preventive effect on ventricular arrhythmias and less toxic action than that of cyclovirobuxine-D and amiodarone (Ami)[4,5], and produced a positive inotropic action on the heart[6]. The main effect of Cyc-A on the action potential in ventricular cells is prolongation of its duration (APD) and effective refractory period (ERP)[4]. At high concentration, Cyc-A reduced the maximal velocity of depolarization (V_{max}) in the use-, frequency-, and voltage-dependent manner[7]. This study was designed to demonstrate the effects of Cyc-A on experimental atrial fibrillation and its electrophysiological mechanisms, and compared them with those of Ami.

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METHODS

Drugs Cycloprotobuxine-A was obtained from Nanjing Xiaoyin Pharmaceutical Co (China); amiodarone from Labaz Laboratory; acetylcholine from Beijing Pharmaceutical Co (China); aconitine and isoprenaline from Sigma; ouabain from E Merck; and adrenaline from Xi-an Pharmaceutical Co (China).

Atrial fibrillation in mice Mice (♂, $n = 41$, $24 \pm s$ 3 g) were anesthetized with sodium pentobarbital 45 $mg \cdot kg^{-1}$ iv and divided into 4 groups. Five min following iv a bolus of the drug tested or an equivalent volume of normal saline, animals were iv given the mixed solution of $CaCl_2$ 60 $mg \cdot kg^{-1}$ and acetylcholine (ACh) 250 $\mu g \cdot kg^{-1}$ to evoke atrial fibrillation.

Atrial fibrilation *in vitro* Guinea pigs of either sex weighing $355 \pm s$ 31 g were stunned. Right atria with the intact sinus node were mounted in a bath that contained 25-mL Tyrode solution gassed with 5 % CO_2 in O_2 (pH 7.4, 36.5±0.5 ℃). Muscles were stretched to an initial resting tension of 300 mg and allowed to equilibrate for 1 h. Surface electrogram of atria was used to detect the development of atrial fibrillation. After atria were treated with Cyc-A or Ami for 30 min, aconitine, ouabain, or adrenaline was added cumulatively in steps of 0.2 $\mu mol \cdot L^{-1}$ every 5 min until atrial fibrillation.

Rhythmic activity in isolated atria The effects of Cyc-A or Ami on the spontaneously beating rate (SBR) in guinea pig right atria with the intact sinus node were determined in

steps of 0.5 lg units per 5 min. SBR was recorded after 4 min of medication. Additionally, 5 groups of 6 right atria each were exposed to isoprenaline (Iso) 10 nmol·L^{-1} after 30 min of perfusion with Cyc-A or Ami at 0.3 or 30 μmol·L^{-1}.

The abnormal rhythmic activity in isolated left atria from guinea pig hearts was elicited by adrenaline[8] before and after the administration of Cyc-A or Ami.

Transmembrane action potentials Isolated guinea pig left atria were placed in 1-mL chamber, and perfused with Tyrode solution aerated with 95 % O_2 + 5 % CO_2 (pH 7.4, 35 ℃)[7]. Atria were stimulated by rectangular pulses of 3 ms in duration and 1.5 times the threshold voltage at a frequency of 1.25 Hz, delivered by an electronic stimulator (Nihon Kohden, SEN-71003). Transmembrane action potentials were recorded by the standard glass microelectrode technique. The output signal obtained from a microelectrode amplifier (Nihon Kohden, MEZ-7101), together with V_{max} from a differentiator (Danyang, BME-1), was displayed on a dual beam oscilloscope to monitor and photograph, and simultaneously fed to a computer for the analysis. The variables of action potential were as follows: resting membrane potential (RP), action potential amplitude (APA), overshoot (OS), V_{max}, and the APD at 50 % and 90 % of repolarization (APD_{50} and APD_{90}).

To observe the effect of Cyc-A on the ACh-induced electro-mechanical activity, one end of isolated atria was pinned in the bath with a fine stainless steel needle; the other end was connected to a force transducer. Both signals of action potentials and contractile force (CF) were recorded simultaneously.

Statistics All data were expressed as $\bar{x} \pm s$. The t test and Fishers exact test were used to analyze statistical significance.

RESULTS

Atrial fibrillation in mice The mixed solution of $CaCl_2$ 60 mg·kg^{-1} and ACh 250 μg·kg^{-1} iv resulted in atrial fibrillation in 9 out of 10 mice. After the iv injection of Cyc-A 1 or 2 mg·kg^{-1} (1/100 LD_{50} or 1/50 LD_{50}[4]), incidences of atrial fibrillation were only 3 or 2 of 10 mice respectively ($P<0.01$). Ami 2.8 mg·kg^{-1} (1/100 LD_{50}[4]) produced a similar protective effect (4 of 11 mice, $P<0.05$).

Atrial fibrillation *in vitro* Cyc-A and Ami concentration-dependently increased the concentration of aconitine, ouabain or adrenaline required to evoke the *in vitro* atrial fibrillation (Tab 1).

Automaticity in isolated atria In isolated right atria with the intact sinus node, Cyc-A and Ami, decreased SBR in a concentration-dependent manner. Within 0.3 − 10 μmol·L^{-1}, both agents produced a slightly inhibitory action. At higher concentrations (> 30 μmol·L^{-1}), both drugs showed stronger effects on automaticity in sinus nodal cells (Fig 1).

Tab 1. Effects of Cyc-A and Ami on atrial fibrillation induced by aconitine, ouabain or adrenaline in isolated guinea pig right atria. $\bar{x} \pm s$. $^{c}P<0.01$ *vs* control; $^{d}P>0.05$, $^{e}P<0.05$ *vs* Cyc-A.

Dose/ μmol·L^{-1}	n	Arrhythmogenic concentration/μmol·L^{-1} Aconitine	Ouabain	Adrenaline
Control	8	0.50±0.19	3.08±0.46	2.07±0.33
Cyc-A 1	8	1.00±0.27^{c}	4.93±0.42^{c}	3.99±0.35^{c}
Ami 1	7	0.86±0.28^{cd}	4.99±0.33^{cd}	3.60±0.24^{c}
Cyc-A 10	8	1.37±0.29^{c}	7.39±0.45^{c}	4.86±0.28^{c}
Ami 10	7	1.08±0.20^{ce}	7.27±0.48^{ce}	4.57±0.30^{c}

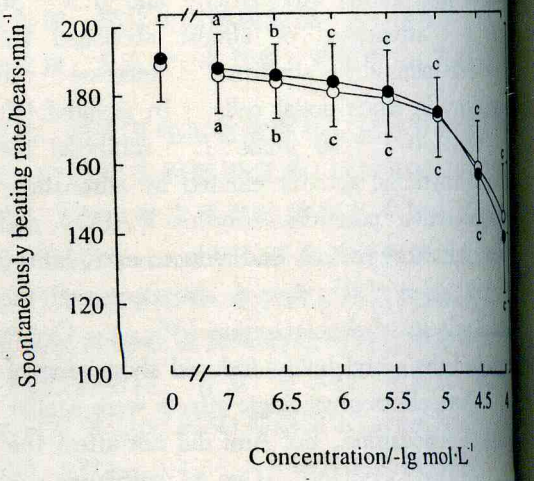

Fig 1. Effects of Cyc-A and Ami on SBR in isolated guinea pig right atria. $n = 7$, $\bar{x} \pm s$. $^{a}P>0.05$, $^{b}P<0.05$, $^{c}P<0.01$ *vs* control.

Iso 10 nmol·L^{-1} markedly increased SBR in sinus nodal cells. After 5-min exposure to Iso, SBR was increased from 202 ± 16 to 314 ± 2 beats·min^{-1} (bpm) ($P<0.01$, $n=6$). Cyc-A prevented the Iso-induced increase in SBR. Compared with that in untreated tissues (5 ± 8 %), the increase in SBR was much less in preparations treated with 0.3 μmol·L^{-1} (42±6 %, $P<0.01$, $n=6$) and with 30 μmol·L^{-1} (1 ± 4 %, $P<0.01$, $n=6$). Ami 0.3 and 30 μm

·L^{-1} also attenuated the Iso action. SBR was increased by 46 ± 6 % and 20 ± 6 %, which were less than that in control ($P<0.05$, $n=6$).

Cyc-A 0.3 and 30 μmol · L^{-1} prominently increased the concentration of adrenaline required to cause the arrhythmia in isolated left atria from 2.2 ±0.6 and 2.5 ± 1.0 μmol · L^{-1} to 3.4 ± 0.9 and 4.7±1.2 μmol·L^{-1}, respectively ($n=7$, $P<0.01$). Ami 0.3 and 30 μmol · L^{-1} displayed a similar action. Following addition of Ami, adrenaline concentrations were increased by 43 ± 9 % and 75 ±21 % ($n=7$, $P<0.01$).

Transmembrane action potentials in isolated atria The prominent effects of Cyc-A on action potentials in isolated left atria were the prolongation in APD. After 30 min of superfusion, Cyc-A 0.3 μmol · L^{-1} lengthened APD_{50} and APD_{90} without changing V_{max}, APA, OS, and RP. At higher concentrations (3 and 30 μmol · L^{-1}), it caused a further increase in APD, associated with a reduction in V_{max} and APA. Ami 0.3 – 30 μmol · L^{-1} elongated APD_{90}, but did not influence V_{max}, APA, OS, RP, and APD_{50} (Fig 2, Tab 2).

ERP in isolated atria ERP was measured by

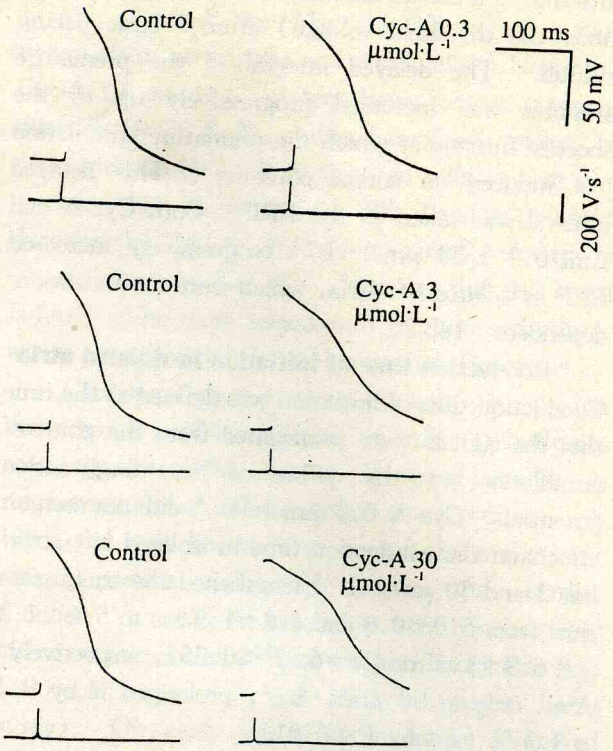

Fig 2. Effects of Cyc-A on transmembrane action potentials in isolated guinea pig left atria.

Tab 2. Effects of Cyc-A and Ami on action potentials in isolated guinea pig left atria. $n=6$, $\bar{x}\pm s$. $^aP>0.05$, $^bP<0.05$, $^cP<0.01$ *vs* before.

	Dose/ μmol·L^{-1}	Cycloprotobuxine-A		Amiodarone	
		Before	After	Before	After
APA/mV	0.3	114 ± 4	112 ± 3[a]	116 ± 3	116 ± 3[a]
	3.0	116 ± 3	110 ± 2[b]	115 ± 5	114 ± 4[a]
	30.0	115 ± 5	105 ± 3[c]	113 ± 4	113 ± 3[a]
OS/mV	0.3	31 ± 3	30 ± 2[a]	31 ± 3	31 ± 2[a]
	3.0	32 ± 2	29 ± 3[b]	32 ± 2	31 ± 2[a]
	30.0	31 ± 2	27 ± 4[c]	30 ± 3	29 ± 2[a]
RP/mV	0.3	−83 ± 3	−82 ± 3[a]	−84 ± 3	−84 ± 3[a]
	3.0	−84 ± 3	−81 ± 2[a]	−84 ± 5	−83 ± 4[a]
	30.0	−84 ± 4	−78 ± 4[c]	−85 ± 5	−84 ± 3[a]
V_{max}/V·s^{-1}	0.3	198 ± 45	190 ± 36[a]	197 ± 33	193 ± 31[a]
	3.0	209 ± 37	182 ± 28[c]	205 ± 42	197 ± 38[a]
	30.0	202 ± 40	164 ± 42[c]	210 ± 36	201 ± 39[a]
APD_{50}/ms	0.3	38 ± 14	41 ± 13[c]	40 ± 9	41 ± 9[a]
	3.0	43 ± 13	52 ± 15[c]	38 ± 12	39 ± 11[a]
	30.0	40 ± 12	55 ± 17[c]	42 ± 13	44 ± 14[a]
APD_{90}/ms	0.3	106 ± 21	119 ± 23[c]	111 ± 23	119 ± 25[c]
	3.0	108 ± 25	137 ± 20[c]	105 ± 27	125 ± 24[c]
	30.0	111 ± 23	186 ± 24[c]	114 ± 21	161 ± 28[c]
ERP/ms	0.3	130 ± 24	156 ± 19[c]	123 ± 16	134 ± 18[c]
	3.0	125 ± 18	161 ± 20[c]	117 ± 19	136 ± 15[c]
	30.0	119 ± 21	168 ± 23[c]	121 ± 22	158 ± 29[c]

introducing a premature stimulus (3 ms duration, .5 times the threshold voltage) after 7 basic pacing stimuli. The delayed interval of the premature stimulus was increased progressively up to the shortest interval at which the premature stimulation just induced an action potential. This delayed interval was taken as the ERP. Both Cyc-A and Ami 0.3 – 30 $\mu mol \cdot L^{-1}$ progressively increased ERP in isolated left atria, which were concentration-dependent (Tab 2).

Conduction time of initiation in isolated atria Conduction time of initiation was defined as the time that the signals were propagated from the point of stimulation to the point of recording action potential. Cyc-A 0.3 $\mu mol \cdot L^{-1}$ did not exhibit effects on the conduction time in isolated left atria, but 3 and 30 $\mu mol \cdot L^{-1}$ lengthened the conduction time from 5.0 ± 0.9 and 4.8 ± 1.3 ms to 5.6 ± 1.2 and 6.8 ± 1.5 ms ($n = 6$, $P < 0.05$), respectively. Ami, only at 30 $\mu mol \cdot L^{-1}$, prolonged it by 9.1 ± 3.3 % ($n = 6$, $P < 0.01$).

Excitability in isolated atria Excitability was judged by the minimal stimulus threshold voltage that could just generate action potentials. Cyc-A and Ami 0.3 – 30 $\mu mol \cdot L^{-1}$ brought about a concentration-dependent increase in the stimulation threshold (Tab 3). It means that both agents may exert an inhibitory effect on the excitability in the atrial cells.

ACh-induced electro-mechanical activity Superfusion of ACh 10 $\mu mol \cdot L^{-1}$ for 5 min significantly shortened the action potential duration and reduced CF, accompanied with a slight decrease in APA and OS in isolated guinea pig left atrial cells. Cyc-A 30 $\mu mol \cdot L^{-1}$ antagonized the ACh-induced shortening of repolarization and decrease in CF, and reduced V_{max} and APA. Ami 30 $\mu mol \cdot L^{-1}$ displayed the similar effect to that Cyc-A, but without affecting V_{max} and APA (Tab 4).

Tab 4. Interactions between Cyc-A or Ami 30 $\mu mol \cdot L^{-1}$ and ACh 10 $\mu mol \cdot L^{-1}$ on action potentials and contractile force (CF) in isolated guinea pig left atria. $n = 6$, $\bar{x} \pm s$. $^aP > 0.05$, $^bP < 0.05$, $^cP < 0.01$ *vs* control; $^dP > 0.05$, $^eP < 0.05$, $^fP < 0.01$ *vs* ACh.

		Control	ACh	ACh + Drug
APA/mV	Cyc-A	113 ± 4	109 ± 4^c	103 ± 5^d
	Ami	111 ± 3	107 ± 4^c	106 ± 4^{cd}
OS/mV	Cyc-A	29 ± 3	25 ± 2^c	23 ± 3^{ce}
	Ami	27 ± 2	24 ± 2^c	23 ± 2^{cd}
RP/mV	Cyc-A	−84 ± 4	−84 ± 4^a	−79 ± 3^d
	Ami	−83 ± 3	−82 ± 3^a	−82 ± 3^{ad}
V_{max}/V·s^{-1}	Cyc-A	197 ± 35	192 ± 39^a	158 ± 27^d
	Ami	194 ± 31	190 ± 33^a	187 ± 32^{ad}
APD_{50}/ms	Cyc-A	38 ± 9	19 ± 5^c	41 ± 13^d
	Ami	37 ± 8	18 ± 5^c	31 ± 7^d
APD_{90}/ms	Cyc-A	107 ± 20	54 ± 12^c	114 ± 27^{bd}
	Ami	103 ± 17	53 ± 11^c	92 ± 15^{cd}
CF/mg	Cyc-A	281 ± 51	28 ± 12^c	308 ± 28^d
	Ami	278 ± 39	32 ± 11^c	223 ± 44^d

DISCUSSION

Our previous papers have shown that Cyc-A produces a preventive effect against various

Tab 3. Effects of Cyc-A and Ami on minimal stimulation voltage (mV) at different stimulation duration in isolated guinea pig left atria. $n = 6$, $\bar{x} \pm s$. $^aP > 0.05$, $^bP < 0.05$, $^cP < 0.01$ *vs* before.

Stimulation duration/ms			0.2	0.5	1.0	2.0	5.0
Cyc-A	0.3 μmol/L	Before	1.46 ± 0.29	0.94 ± 0.13	0.80 ± 0.14	0.70 ± 0.10	0.66 ± 0.12
		After	1.78 ± 0.34^c	1.08 ± 0.15^c	0.91 ± 0.13^c	0.74 ± 0.12^b	0.67 ± 0.13^a
Ami	0.3 μmol/L	Before	1.50 ± 0.32	0.96 ± 0.16	0.77 ± 0.11	0.73 ± 0.13	0.62 ± 0.09^a
		After	1.77 ± 0.37^c	1.08 ± 0.22^c	0.83 ± 0.16^c	0.76 ± 0.14^b	0.63 ± 0.10^a
Cyc-A	3.0 μmol/L	Before	1.49 ± 0.25	0.97 ± 0.11	0.81 ± 0.13	0.71 ± 0.11	0.65 ± 0.09
		After	2.13 ± 0.16^c	1.24 ± 0.16^c	0.99 ± 0.15^c	0.76 ± 0.13^c	0.69 ± 0.08^a
Ami	3.0 μmol/L	Before	1.45 ± 0.26	0.93 ± 0.18	0.79 ± 0.17	0.68 ± 0.15	0.63 ± 0.11
		After	1.81 ± 0.22^c	1.11 ± 0.15^c	0.91 ± 0.14^c	0.71 ± 0.12^b	0.66 ± 0.12^b
Cyc-A	30.0 μmol/L	Before	1.43 ± 0.31	0.92 ± 0.15	0.78 ± 0.14	0.71 ± 0.12	0.65 ± 0.11
		After	2.46 ± 0.30^c	1.35 ± 0.17^c	1.02 ± 0.16^c	0.80 ± 0.13^c	0.71 ± 0.09^a
Ami	30.0 μmol/L	Before	1.47 ± 0.24	0.95 ± 0.14	0.82 ± 0.15	0.67 ± 0.11	0.64 ± 0.08
		After	2.19 ± 0.33^c	1.24 ± 0.21^c	1.01 ± 0.17^c	0.72 ± 0.15^c	0.67 ± 0.11^b

experimental ventricular arrhythmias[4,5]. In the present study, this alkaloid has been demonstrated, significantly and dose-dependently, to reduce incidences of *in vivo* atrial fibrillation in mice and to increase the concentration of aconitine, ouabain or adrenaline required to elicit atrial fibrillation in isolated guinea pig right atria with the intact sinus node. Compared with Ami, Cyc-A produces more potent or similar anti-arrhythmic effects in both ventricular[4,5] and atrial tissue (this study), and has a greater therapeutic index[4]. Moreover, Ami shows a wide range of side effects, especially at higher doses, some of which (eg, pulmonary fibrosis and hepatoxicity) may be potentially lethal. Even so, because of its highly potent therapeutic effect and wide spectrum, this drug is still used to treat cardiac arrhythmias that are resistnat to other conventional drugs or very serious[9]. Thus, Cyc-A might be worthy while further studying.

It is widely accepted that important electrophysiological mechanisms responsible for tachycardia are an increase in the discharge of the pacemaker cell, the generation of abnormal impulse, a shortening in repolarization, and an increase in excitability[10]. Similar to Ami, Cyc-A inhibited the spontaneously beating rate, particularly the isoprenaline-induced abnormal increase, in the isolated right atria with the intact sinus node. The abnormal automaticity induced by adrenaline in isolated left atrial muscles was also inhibited by this compound. Cyc-A 0.3 – 30 $\mu mol \cdot L^{-1}$ prolonged the action potential duration and effective refractory period and decreased the excitability in isolated atria. Therefore, these could be contributed to its protection against atrial fibrillation.

The further slowing of impulse conduction can convert the unidirectional block, which represents one of the most important causes of re-entrant tachycardia, into the bidirectional block, by that canceling or interrupting the reentry[10]. Although at lower concentration (0.3 $\mu mol \cdot L^{-1}$), Cyc-A had no effects on V_{max} and conduction time in atrial cells, higher concentration (> 3 $\mu mol \cdot L^{-1}$) produced an inhibitory action on them. Ami (0.3 – 30 $\mu mol \cdot L^{-1}$) were without effects. These results suggest the antifibrillatory action of Cyc-A, not Ami, in atrial tissue could be associated, in part, with the effect on impulse conduction.

Cyc-A had the identical effects on action potentials in ventricular and atrial cells. However, Cyc-A (3 $\mu mol \cdot L^{-1}$) lengthened action potential duration by 26.8 %, reduced maximal velocity of depolarization by 12.9 % in atrial cells, which was stronger than in ventricular cells (action potential duration by 16.8 % and maximal velocity of depolarization by 7.0 %). It means that this agent is likely to be more selective in the anti-arrhythmic action against atrial tissue than ventricular tissue.

Cardiac function in many patients with cardiac arrhythmias is of low status. Cardiac arrhythmias may aggravate the exiting abnormal change in hemodynamics or induce cardiac decomposition. It has been well known that many anti-arrhythmic drugs possess inhibitory action on cardiac function[11]. Cyc-A exerted a positive inotropic effect on myocardium[6] and antifibrillatory action in ventricular tissue[4,5] and in atrial tissue (this study). Obviously this is its advantage compared with other most anti-arrhythmic drugs, which could be useful as the hearts in need of anti-arrhythmic therapy are often also failing.

The acetylcholine-induced shortening of action potential and reduction of contractile force in atrial muscles are mainly attributed to the activation of the muscarinic potassium current and the inhibition of the slow inward calcium current[12]. In this study, we found Cyc-A could reverse the above-mentioned electro-mechanical activity induced by acetylcholine. This result, together with the fact that this alkaloid exerts an augmentation of contractile force and a positive staircase effect[6] as well as prolongation of action potential duration (including a plateau phase) in ventricular cells[4,6,7] and atrial cells (this study), leads to the suggestion that it might at least enhances the slow inward calcium current, which could be one of the important ion bases for its effects.

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环原黄杨星 A 对心房纤颤的作用

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关键词 环原黄杨星 A；胺碘酮；心房纤颤；动作电位；心房

目的：研究环原黄杨星 A (Cyc-A)抗心房纤颤的作用. **方法**：用药物诱发心房纤颤；用微电极技术记录动作电位. **结果**：Cyc-A 对抗 $CaCl_2$-ACh 诱发的在体心房纤颤和乌头碱等诱发的离体心房纤颤，并与胺碘酮作用相似. Cyc-A 抑制窦房结细胞的自律性和异丙肾上腺素引起的自律性增加. 对离体左心房，Cyc-A 抑制肾上腺素引起的异常自律性，延长 APD 和 ERP，降低兴奋性；高浓度时还可降低 V_{max}. Cyc-A 能拮抗 ACh 所致的 APD 缩短. 胺碘酮有相似的作用，但对 V_{max} 无影响. **结论**：Cyc-A 抗心房纤颤的作用是通过延长复极、降低自律性和抑制兴奋性而产生.

《心血管药理学》第 2 版出版

人民卫生出版社出版的由陈修主编，26 位国内专家编写的《心血管药理学》第 1 版于 1989 年出版后，深受广大读者好评.

《心血管药理学》第 2 版增加陈维洲与曾贵云两位著名的心血管药理学家为主编，增聘了 16 位心血管临床与心血管药理学专家参加写成. 新版增加了心血管膜离子通道，血管内皮细胞药理学，肾上腺素受体与心血管病的基因治疗等六章新内容. 介绍了近年来细胞与分子生物学研究在心血管药理学的新成果. 为加强临床应用，抗高血压药，抗心律失常药与利尿药等章分为基础理论与临床两部分内容. 根据现实需要，对防治脑血管病的新药作了重点介绍与评价，是目前我国唯一的一本心血管药理学专著. 书末附录的新药一览表，列出了 1989 到 1995 年世界首次上市或正在临床研究的 106 种心血管新药.

新版 100 余万字，精装，定价 90 元. 请与 200433 上海第二军医大学药理教研室苏定冯教授，200031 上海中国科学院上海药物研究所陈维洲研究员，100051 北京中国医学科学院药物研究所曾贵云研究员，410078 长沙湖南医科大学陈修教授，510100 广州广东省心血管研究所林曙光教授联系.