Blockade of α_1-Adrenoceptors and Cardiac Depressant Effect by a Newly Synthetic Antihypertensive Drug, DL-017 of Quinazoline Derivative

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Abstract

The electromechanical effects of 3-[[4-(2-methoxyphenyl)piperazin-1-yl]methyl]-5- (methylthio)-2,3-dihydroimidazo[1,2-c]quinazoline (DL-017), a newly synthesized quinazoline-derived antihypertensive agent, on mammalian cardiac tissues were evaluated. In driven canine Purkinje fibers, DL-017 decreased twitch tension, the maximal rate of upstroke of the action potential ($\dot{V}_{max}$), and intracellular Na^+ activity (a^i_{Na}) in a concentration-dependent manner. The action potential duration was decreased in canine Purkinje fibers but increased in guinea pig papillary muscles. In guinea pig ventricular papillary muscles, phenylephrine in the presence of 1 μM propranolol increased the twitch tension in a concentration-dependent manner. At 10 μM, phenylephrine significantly decreased a^i_{Na} and shortened the action potential duration. DL-017 at 0.01 μM inhibited these phenylephrine-induced effects and shifted the concentration-dependent curve to the right. In sinoatrial nodes, DL-017 inhibited pacemaker activity, involving decreases in the slope of diastolic depolarization and $\dot{V}_{max}$ and an increase in a delay of repolarization. These results suggest that, in addition to blockade of α_1-adrenoceptors and Na^+ channels, DL-017 reduces cardiac excitability and contractility in association with inhibition of slow inward Ca^{2+} and outward K^+ channels. Since two order higher concentrations are required, the contribution of DL-017 to cardiac depressant from blockade of ionic channels seems to be less important when this compound is clinically used as an antihypertensive drug.

Key words: arrhythmia, α_1- adrenoceptor antagonist, quinazoline, Na^+ activity

Introduction

The discovery of new and effective antihypertensive agents is important in improving treatment of hypertension and reducing the risk of cardiovascular morbidity and mortality (6, 25). The use of α_1-adrenergic blockers has been proved to have several therapeutic benefits, which go beyond blood pressure management, such as improvements in lipid

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Received May 7, 2001; Revised June 8, 2001; Accepted June 13, 2001.

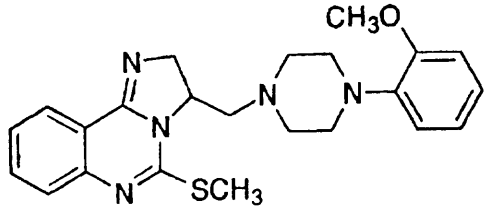

Fig. 1. Chemical structure of DL-017

profile, diabetes mellitus status, benign prostatic hyperplasia, and even sexual function (9, 10). Recently, our synthetic studies focused on a group of tricyclic condensed quinazoline derivatives, and revealed that 2,3-dihydroimidazo[1.2- c]quinazolin-5(6H)-one derivatives with an appropriate arylpiperazine side chain could effectively lower blood pressure and possessed antagonistic action on α_1-adrenoceptors (4, 5). Pharmacological evaluation revealed that these derivatives competitively antagonized phenylephrine-induced vasoconstriction and inositol monophosphate formation, and also improved lipid profile in rats with high lipid diet (4, 7, 24).

In spontaneously hypertensive rats, quinazoline derivatives, as well as prazosin, decreased blood pressure without reflex tachycardia for more than 2-h (24). Of these compounds, (3-[[4-(2-methoxyphenyl) piperazin-1-yl]methyl]-5-(methylthio)- 2,3-dihydroimidazo[1,2c]quinazoline (DL-017; Fig. 1) was the most highly selective and potent α_1-adrenergic antagonist, with an inhibitory constant (K_i) of 0.90±0.08 nM, and is undergoing clinical trial as an antihypertensive drug in Taiwan (4). In addition to α_1-adrenergic antagonism, DL-017 inhibited [^{3}H]batrachotoxin binding to Na^+ channels in the rat brain with IC_{50} of 450 nM and K_i of 404 nM in a ligand-binding assay (a screening test serviced by Panlabs Pharmacology Service). The preliminary result suggested that DL-017 could block α_1-adrenoceptors and Na^+ channels. However, the relative contribution of α_1-adrenoceptor blockade and Na^+ channel blockade to the inhibitory effect on the cardiac tissues is not evaluated. In addition, whether DL-017 could directly inhibit the pacemaker activity was still unknown.

The aim of this work was to evaluate the electrical and mechanical effects of this newly synthesized α_1-antagonist, DL-017, on mammalian cardiac tissues. The α_1-adrenoceptor antagonistic action on the ventricular muscle and direct inhibition of the pacemaker activity were assessed. Changes in action potentials were analyzed to explain the possible cellular mechanism of cardiac depressant action exerted by DL-017.

Table 1. Antagonistic Effects of DL-017 in the Ventricular Papillary Muscle of Guinea Pig Hearts

	n	RMP, mV	APD_{90}, ms	V_{max}, V/s	a^i_{Na}, mM	TT, %
Control	7	-83±1	207±7	193±4	6.0±0.5	100
PPL 1 μM		-83±2	207±7	194±6	5.9±0.5	92±4[a]
PPL 1 μM + PE 10 μM		-83±2	203±8[a]	193±6	5.6±0.4[a,b]	117±5[a,b]
Control	5	-84±2	212±6	196±3	6.0±0.5	100
PPL 1μM + DL-017 0.01 μM		-84±2	210±7	193±4	5.8±0.5	88±5[a]
PPL 1 μM + DL-017 0.01 μM + PE 10 μM		-83±1	210±7	189±3	5.9±0.9	88±4[a]

Values are Mean±SEM. [a]: $P<0.05$ vs. control; [b]: $P<0.05$ vs. PPL-treated group; PPL= propranolol; PE= phenylephrine; RMP= resting membrane potential; APD_{90}= duration at 90% repolarization; a^i_{Na}= intracellular Na^+ activity; TT= twitch tension.

Materials and Methods

Biological Preparations

Mongrel dogs (5-10 kg, either sex) or male guinea-pigs (250-450 g) were sacrificed by exsanguinations from the femoral artery after pentobarbital anesthesia (50 mg/kg,i.v. for dogs and i.p. for guinea-pigs). A strand of fine Purkinje fibers from a dog heart or a papillary muscle of the right ventricle of a guinea pig heart, approximately 0.5 -1 mm in diameter and 3-5 mm in length, was carefully dissected and then mounted in a narrow perfusing chamber. The superfusing Tyrode solution was oxygenated with a gas mixture of 97% O_2 and 3% CO_2, to give a pH of 7.4, and was maintained at 37 °C. The composition of the solution was (in mM) NaCl 135, KCl 5.4, $CaCl_2$ 1.8, $NaHCO_3$ 12, $MgCl_2$ 1.1, NaH_2PO_4 0.5, and glucose 5.0. In studies of action potential and intracellular Na^+ activity (a^i_{Na}), the muscle fiber driven at 1 Hz was fixed with two L-shaped insect pins. One end of the muscle fiber was fixed and driven with a Grass stimulator. The other end was tied to a force displacement transducer (Cambridge, model 403A) to measure tension. The muscle fiber was stretched until the twitch force was about 60% of the maximum. The sensitivity of the transducer was adjusted to 30 mV/mg. Na^+-selective and conventional microelectrodes were implanted in cells between the

insect pins, where the twitch displacement was not vigorous, to monitor changes of action potential and a^i_{Na}. In the study of pacemaker potential, the sinoatrial node preparation was perfused with solution containing 4 mM K^+ and 2.7 mM Ca^{2+}.

Preparation of Microelectrodes and Measurement of a^i_{Na}

The Na^+-selective and conventional microelectrodes were made from borosilicate micropipettes. The conventional microelectrode had a tip resistance in the range 10-40 MΩ when backfilled with 3 M KCl solution. The action potential was displayed on an oscilloscope (Gould model 1600). The $\dot{V}_{max}$ was measured after the action potential signal was passed through a differential amplifier. The Na^+-selective microelectrode was beveled and backfilled with 100 mM NaCl after silanization with a tiny amount of n-tributylchlorosilane. A 100-300 μm column of Na^+-selective liquid sensor (Fluka) was drawn into the tip. The sodium electrode was calibrated using single-electrolyte solutions containing 100, 10, 1 mM NaCl, or 100 mM KCl, separately, after each experiment. The potential response of Na^+-electrodes was 58.6±0.5 mV (n=42) per tenfold sodium activity change at 37°C (22). The selectivity coefficient for K^+ (k_{NaK}) was less than 0.02. Since the Na^+- electrode did not usually respond to changes in intracellular Ca^{2+} activity (a^i_{Ca}) below 1 μM, the interference of a^i_{Ca} was ignored (2, 12). Signals from the conventional and Na^+-selective microelectrodes passed through two identical low-pass filters with a fixed frequency of 0.2 Hz (A.P. Circuit Corp). The electrical potential of the sodium electrode (E^i_{Na}) and conventional electrode ($\overline{V}m$) and their difference (a^i_{Na}) were recorded on a chart recorder. The intracellular Na^+ activity of muscle fibers was calculated according to a modified Nicolsky equation (12):

$$E^i_{Na} - \overline{V}m = E_o + S \log[a^i_{Na} + k_{NaK} a^i_K],$$

where E^i_{Na} and $\overline{V}m$ are the respective potentials of sodium and conventional electrodes in cells. E_o is the constant potential of the electrometric system. S is the slope of potential response in calibration solutions for each electrode. a^i_K is the intracellular K^+ activity and the reported value of 116 mM in cardiac ventricular muscles was used for calculation (2). Since the selective coefficient for K^+ was quite low, the interference in changes of a^i_K were neglected in this study (12, 17).

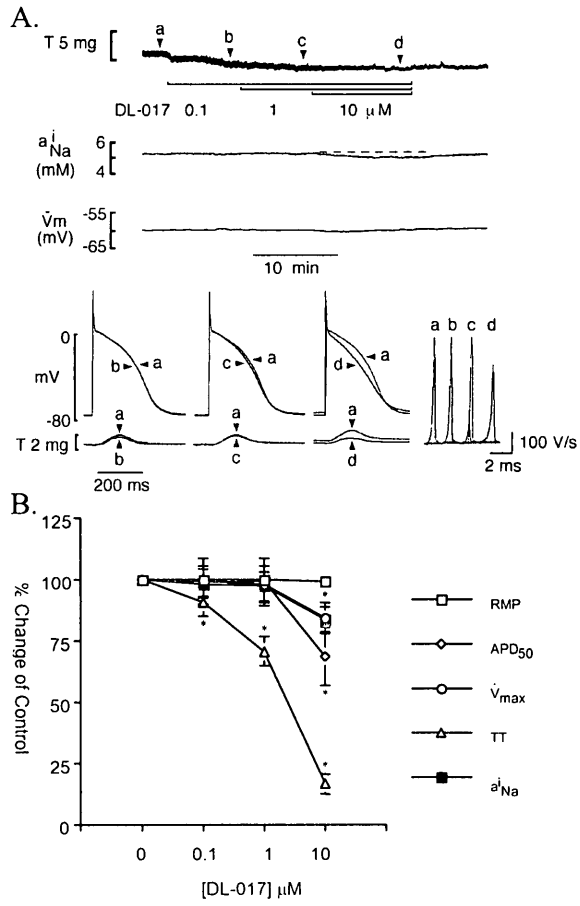

Fig. 2. (A) Simultaneous recordings of twitch tension (T), intracellular Na^+ activity (a^i_{Na}), and mean membrane potential ($\overline{V}m$) in a cardiac Purkinje fiber. Action potentials and maximal rate of depolarization ($\dot{V}_{max}$) were taken as indicated a, b, c, and d. (B) Summarized data of five cardiac Purkinje fibers. The control values of resting membrane potential (RMP), duration of 50% repolarization (APD_{50}), $\dot{V}_{max}$, and a^i_{Na} were indicated in text. *: $P<0.05$.

Drugs and Data Analysis

Phenylephrine hydrochloride was purchased from Sigma. DL-017, synthesized in and provided from the laboratory of Dr. JW Chern were dissolved in dimethyl sulfoxide (DMSO) to make stock solutions of 0.1 M. In this study DMSO was less than 0.1 %, in which concentration the electromechanical event was not affected. The experimental data were pooled for analysis. Only those experiments in which the recovery reached at least 80% of the control level during washing out were included. Student's t-test or Newman-Keul

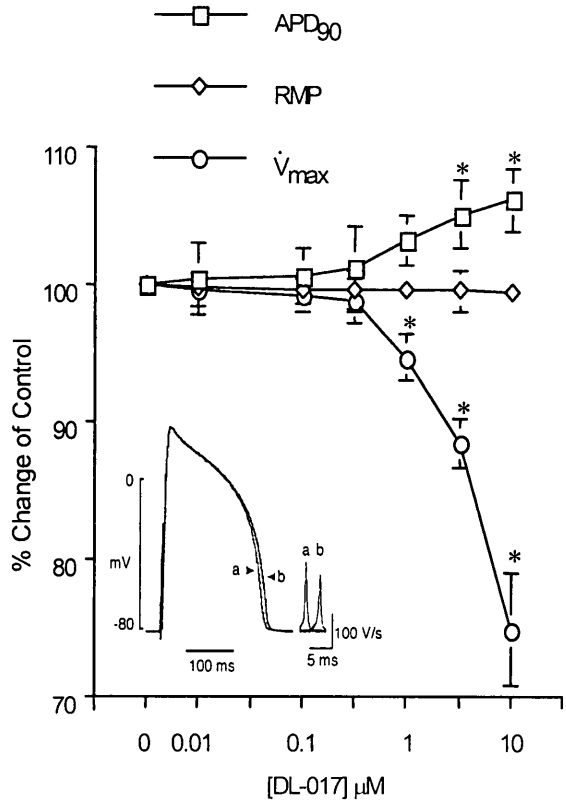

Fig. 3. Concentration dependent curve for changes of the action potential of guinea-pig ventricular papillary muscles in response to DL-017. Insertion of the superimposed action potentials is an example of the control (a) and the experiment after10 mM DL-017 (b).

test was employed to analyze the experimental data. The difference was considered significant when the P value was less than 0.05.

Results

Effects of DL-017 on Canine Cardiac Purkinje Fibers

We examined the electromechanical effects of DL-017 on the canine cardiac Purkinje fiber. As shown in Fig. 2A, DL-017 decreased the twitch tension and resting tension in a concentration-dependent manner. The action potential duration, especially at 50% repolarization (APD_{50}), the maximal rate of rise of the action potential ($\dot{V}max$), and a^i_{Na} were insignificantly changed until concentrations of DL-017 were greater than 1 μM. In 5 fibers, the control values of resting membrane potential (RMP), duration of 50% repolarization (APD_{50}), $\dot{V}_{max}$, and a^i_{Na} were -74.2±2.4 mV, 233.9±12.3 ms, 409.3±25.3 V/s, and 7.4±0.5 mM,

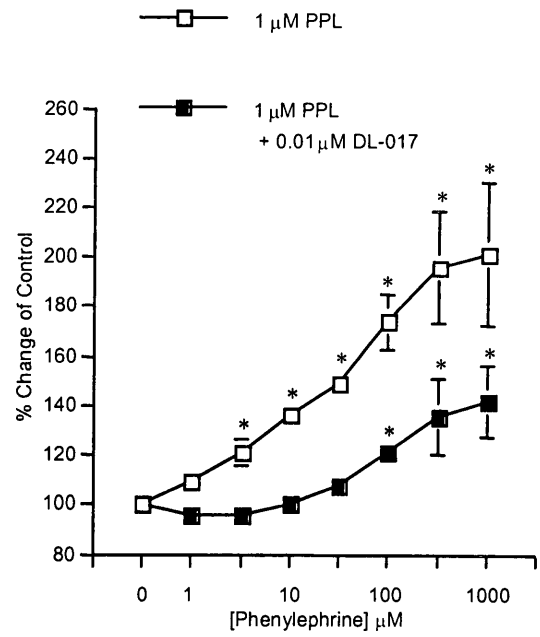

Fig. 4. Concentration-dependent curve for changes of the twitch tension of guinea pig ventricular papillary muscles in response to phenylephrine in the presence and absence of 0.01 μM DL-017. Phenylephrine was cumulatively administered. PPL: propranolol. n=8 in each group. *P<0.01.

respectively. At 10 μM DL-017, the twitch tension reduced nearly by 80% and APD_{50} shortened by 30 % of the control. The $\dot{V}max$ and a^i_{Na} were both reduced by 26% of the control (Fig. 2B).

Effects of DL-017 on Guinea Pig Ventricular Papillary Muscle

The effects of DL-017 on the action potential were examined in 8 guinea pig ventricular papillary muscles. As shown in Fig. 3, DL-017 did not exert any significant effect until the concentration was up to 1 μM. The parameters of the action potential included RMP, APD_{90}, and $\dot{V}max$ were –81.8±0.9 mV, 216.7±11.8, and 200.5±3.7 V/s, respectively, in the control condition. When concentrations were greater than 1 μM, DL-017 significantly decreased $\dot{V}max$ and increased APD_{90} in a concentration-dependent manner.

Stimulation of α_1-adrenergic receptors by phenylephrine could potentate the twitch tension with a reduced a^i_{Na} in guinea pig ventricular papillary muscles. In Fig. 4, phenylephrine in the presence of 1 μM propranolol increased the twitch tension of 8 muscle

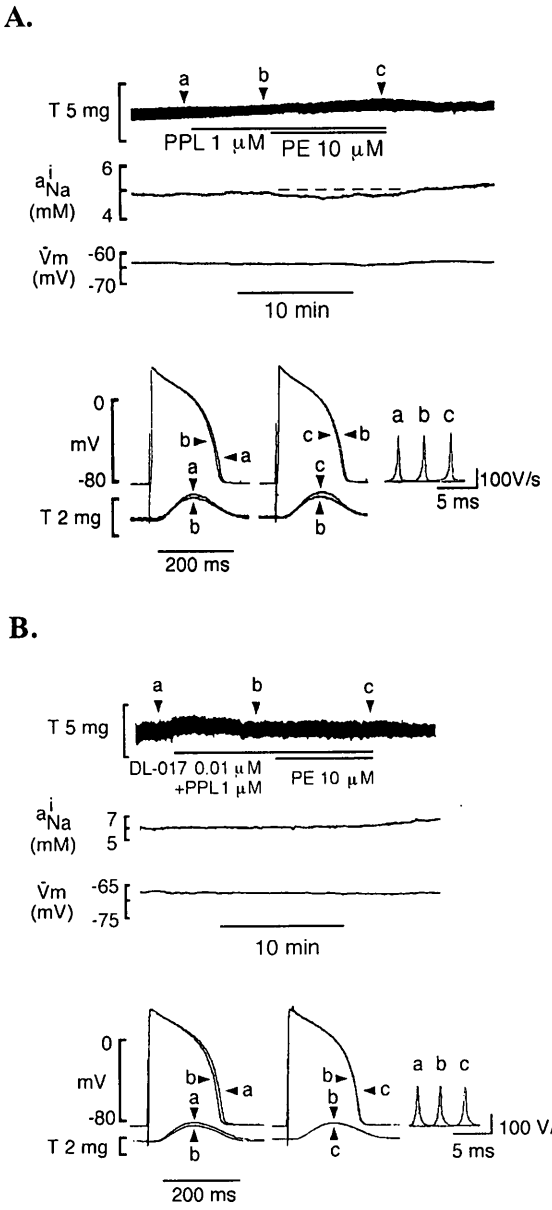

Fig. 5. Electrical and mechanical effects of DL-017 on guinea pig ventricular papillary muscles. (A) Effects of phenylephrine (PE) in the presence of propranolol (PPL). (B) Effects of phenylephrine in the presence of propranolol and DL-017. Abbreviations and recordings are the same as in Fig. 1.

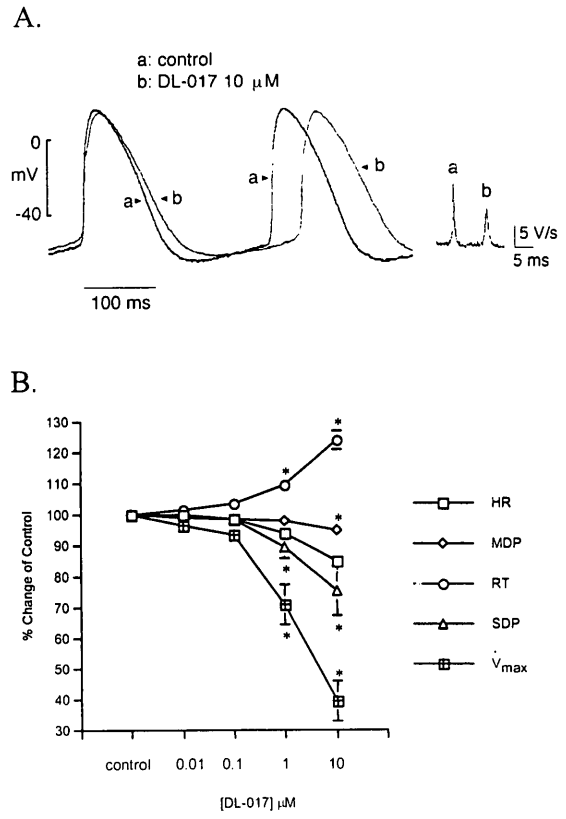

Fig. 6. Effect of DL-017 on the action potentials of sinoatrial node cells. (A) Superimposed action potentials were recorded before and after 10 mM DL-017 for 10 min. (B) Concentration-dependent changes of the maximal diastolic membrane potential (MDP), the repolarization time (RT), the slope of diastolic depolarization (SDP), and maximal upstroke velocity of the spike potential ($\dot{V}_{max}$) in the action potential in eight sinoatrial nodes were analyzed. Administration of DL-017 was accumulated. N=8; *p < 0.05.

fibers in a concentration dependent manner when concentrations were greater than 1 μM. DL-017 at 0.01 μM shifted the curve to the right and inhibited the positive inotropic response until 30 μM phenylephrine. In addition to the increased twitch tension, 10 μM phenylephrine in the presence of 1 μM propranolol decreased the APD_{90} and a^i_{Na} without change in $\dot{V}_{max}$ (Fig. 5A). While the muscle fiber was pretreated with 0.01 μM DL-017 and 1 μM propranolol, 10 μM phenylephrine no longer produced any significant effect (Fig. 5B). In 7 papillary muscles, changes in the action potential and a^i_{Na} after 1 μM propranolol were not statistically significant, but the twitch tension was significantly decreased by 8 %. In the presence of 1 μM propranolol, phenylephrine at 10 μM increased twitch tension by 25 % and further significantly decreased a^i_{Na} by 0.3 μM. Changes in the action potential were not significant except for a decreased APD_{90} (Table 1). In another 5 papillary muscles pretreated with 0.01 μM DL-017 and 1 μM propranolol, the twitch tension decreased significantly. A subsequent application of 10 μM phenylephrine produced no significant effects on the action potential, twitch tension, or a^i_{Na} (Table 1).

Effects of DL-017 on Pacemaker Activity

The effect of DL-017 on pacemaker activity of sinoatrial nodes was examined in 8 guinea-pigs. Parameters of the pacemaker activity included rhythm, maximal diastolic potential, duration of repolarization, slope of diastolic depolarization, and maximal upstroke velocity of the spike potential in the control condition were 208.3±5.6 bpm, 63.8±1.0 mV, 127.0±2.6 ms, 89.7±6.8 mV/s, and 20.8±5.5 V/s, respectively. It can be inferred from Fig. 6 that DL-017 inhibited the pacemaker activity in a concentration-dependent manner. The inhibitory effect, associated with increased duration of repolarization and decreased rate of diastolic depolarization, was significant whenever concentrations of DL-017 were greater than 1 mM. At 10 μM, DL-017 significantly decreased the frequency of pacemaker activity by 25%. The maximal diastolic potential was significantly elevated by 3.0±0.5 mV. The duration of repolarization from the peak of upstroke to the maximal diastolic potential was significantly increased by 24.0±4.2 ms. The rate of diastolic depolarization and the maximal upstroke velocity of the spike potential were significantly decreased by 25 and 60 %, respectively.

Discussion

We have described some of the pharmacological effects of DL-017, a novel antihypertensive quinazoline derivative, on cardiac tissues. Our findings indicate that: (i) DL-017 exerts a directly inhibitory effect on cardiac Purkinje fibers. The decreased twitch force is in a concentration-dependent manner, and is involved in decreases in $\dot{V}_{max}$ and a^{i}_{Na} when concentrations of DL-017 exceed the micromolar range; (ii) DL-017 blocks the α_1-adrenergic effect of phenylephrine at submicromolar concentrations; (iii) DL-017 directly decreases pacemaker activity of sinoatrial nodes in which the maximal upstroke velocity of the spike potential, the slopes of diastolic depolarization, and the rate of repolarization of the action potential are inhibited.

Studies of α_1-adrenoceptor antagonists have demonstrated that DL-017 as well as prazosin is a relative highly selective and potent α_1-adrenoceptor antagonist and can reduce blood pressure with similar efficiency in vivo (4). DL-017 like prazosin also possesses class I antiarrhythmic action with a decrease in $\dot{V}_{max}$ in guinea pig cardiac ventricular papillary muscles when concentrations are greater than 1 μM (14, 23). In ligand binding assay, DL-017 inhibited [^{3}H]batrachotoxin binding to Na^+ channels in the rat brain with IC_{50} of 450 nM and K_i of 404 nM (4). In the present studies, DL-017 at nanoomolar range was found to antagonize the effects of phenylephrine on cardiac tissues, but did not decrease $\dot{V}_{max}$ and a^{i}_{Na} until concentrations were larger than 1 μM. These findings, in consistent with our previous study, suggests that the contribution of the relative blockade of α_1-adrenoceptors to the drug effects is greater than the blockade of Na^+ channels (4).

In the cardiac Purkinje fiber as well as guinea-pig ventricular papillary muscle, DL-017 could decrease the twitch and diastolic tension without alteration of the action potential and a^{i}_{Na} when the concentration was below 1 μM, suggesting a direct inhibition of the contractility (23). Significant changes in the action potential and a^{i}_{Na} were found only when the concentration of DL-017 was greater than 1 μM. The action potential duration was shortened in the cardiac Purkinje fiber but prolonged in the guinea-pig ventricular papillary muscle. This difference might be due to species variation. In cardiac Purkinje fibers, a TTX-sensitive "window" plateau current existed and contributed to the action potential duration in a great extent (1). DL-017, like other local anesthetics, at high concentrations could inhibit the TTX-sensitive Na^+ current in vascular smooth muscle cells (unpublished results) and decreased the $\dot{V}_{max}$ and a^{i}_{Na} in cardiac tissues (1, 18). Therefore, the shortening of the action potential duration possibly resulted from the inhibitory effect of DL-017 on TTX-sensitive "window" plateau currents. In our previous study, DL-017 decreased the twitch tension of the guinea-pig ventricular papillary muscle but did not affect the slow action potential in the isoproterenol-containing high K^+ solution, suggesting an insignificant effect on the Ca^{2+} current. The prolongation of the action potential duration, especially at 90% repolarization, in guinea pig ventricular papillary muscles was possibly attributed to inhibition of delayed rectifier K^+ channels.

In addition to β-adrenoceptors, mammalian myocardium possess α_1-adrenoceptors. Phenylephrine has a higher affinity for myocardial α_1-adrenoceptors than for β-adrenoceptors (3, 19). Stimulation of α_1-adrenoceptors can shorten the action potential duration by activation of K^+ currents, enhance the contractile force by increasing intracellular Ca^{2+} and the sensitivity of contractile protein to Ca^{2+}, and decrease a^{i}_{Na} by activation of Na^+-K^+ pump (8, 20, 21). Propranolol, despite its β-antagonistic effect, can inhibit Na^+ channels (11). In the present study, phenylephrine increased the twitch tension with a shortening of the action potential duration and a decreased a^{i}_{Na} after inhibition of β-adrenoceptors with propranolol. These actions were mediated by activation of α_1-adrenoceptors. DL-017 at

0.01μM did not have any direct effect but completely abolished all the actions of phenylephrine, suggesting the blockade of α_1-adrenoceptors.

In sinoatrial nodes, the ionic mechanism of pacemaker activity is usually referred to a preliminary decay of K^+ conductance and slow activation of cation channels, mostly associated with Na^+ and Ca^{2+} (13, 15, 16). Thus, activation of funny current (I_f) and of L-type Ca^{2+} current constitutes the slow diastolic depolarization during normal pacemaker activity. In the present study, DL-017 decreased the pacemaker activity, especially in high concentrations. Of the action potential, the maximal rate of the upstroke, the slope of the diastolic potential, and the rate of repolarization were decreased. These findings suggest that the negative inotropic effect of DL-017 was most likely due to inhibition of the L-type Ca^{2+} currents and delayed outward K^+ currents.

In conclusion, we have demonstrated that DL-017 is a very potent α_1-adrenoceptor antagonist. Clinically, patients with a sustained hypertension are subject to ischemic heart disease, which is often associated with heart failure and cardiac arrhythmia. The inhibitory action of α_1-adrenoceptor antagonists can reduce the vascular tone and myocardial excitability but, at higher dose, may blockade Na^+, Ca^{2+}, and K^+ channels and worsen cardiac inotropic and chronotropic function. DL-017 is safely used as an antihypertensive drug because the adverse cardiac depressant effect requires two order higher concentrations.

Acknowledgements

We thank Dr. H.-H. Wang of Columbia University for reading and editing this manuscript. This work was supported by grants from Armed Forces Taoyuan General Hospital (AFTGH-8903), and the National Science Council (NSC85-2331-B016-022 M04), ROC.

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