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Time- and Voltage-dependent Effects of Disopyramide on Maximum Upstroke Velocity of Cardiac Action Potentials

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Abstract The effect of disopyramide on maximum upstroke velocity ($\dot{V}_{max}$) of cardiac action potential was studied with particular reference to its time- and voltage-dependence. The time-dependence (recovery process of $\dot{V}_{max}$ during diastolic interval) was assessed by introducing premature stimuli or by interrupting stimuli. The voltage-dependence was examined by changing the external K^+ concentration ($[K^+]_0$). In the presence of the drug, the recovery process of $\dot{V}_{max}$ slowed at high $[K^+]_0$ in early stages and at low $[K^+]_0$ in late stages during the diastolic interval. Relevance of the present findings to clinical utility of disopyramide as an antiarrhythmic agent was discussed.

Key Words: Heart; caraiac action potential, maximum upstroke velocity, Antiarrhythmic agentsy, disopyramide

Introduction

It is well known that both the actions of a local anesthetic drug on the neuronal membrane and those of a quinidine-like drug on the cardiac tissues are manifested more markedly at high rates of stimulation (time-dependence). Both of these actions are also affected by the membrane potential (voltage-dependence)[1]. The quinidine-like drugs are considered to suppress the fast Na^+ inward current. In the studies with the heart, maximum upstroke velocity of action potential ($\dot{V}_{max}$) has been regarded as a useful measure of the fast Na^+ current, and, hence ,one can observe the quinidine-like actions as a reduction of $\dot{V}_{max}$. However, because of the time-dependent property of the action, the reduced-upstroke velocity of the action potential of cardiac tissues driven at a constant cycle length is restored after a long pause of stimulation. The time-dependent recovery of $\dot{V}_{max}$ during a diastolic interval has been termed as "recovery process of $\dot{V}_{max}$. 'On the other hand, the quinidine-like drugs suppress the electrical activities of nerve and cardiac cells more strongly with the low membrane potentials than with normal resting membrane potentials. Hence, in the properly chosen concentrations of the

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drug the depression of excitability occurs only in the ischemic myocardial cells where the membrane potentials are reduced. Thus all the quinidine-like drugs so far examined have been shown to produce both time- and voltage-dependent actions.

The efficacy of disopyramide in the treatment of cardiac arrhythmias has been well documented[2]. In the previous paper[3], it was demonstrated that 20 μM disopyramide affected $\dot{V}_{max}$ in guinea-pig papillary muscles. The effect of disopyramide was dependent on $[K^+]_0$. Therefore, in the presence of the drug, an elevation of $[K^+]_0$ would slow the recovery process of $\dot{V}_{max}$ at short diastolic intervals ($<$1 sec), but would accelerate the process at long diastolic intervals ($>$10 sec). The recovery-slowing property of disopyramide is similar to that reported for lidocaine[4),5]. The recovery-accelerating property as observed with disopyramide, on the other hand, has not been reported for any other antiarrhythmic drugs. In the present experiments, therefore, we examined the recovery process of $\dot{V}_{max}$ at diastolic intervals of up to 2 min in the presence of 20 μM disopyramide under various external potassium concentrations.

Materials and Methods

Electrophysiologic techniques

Techniques for preparing experimental materials

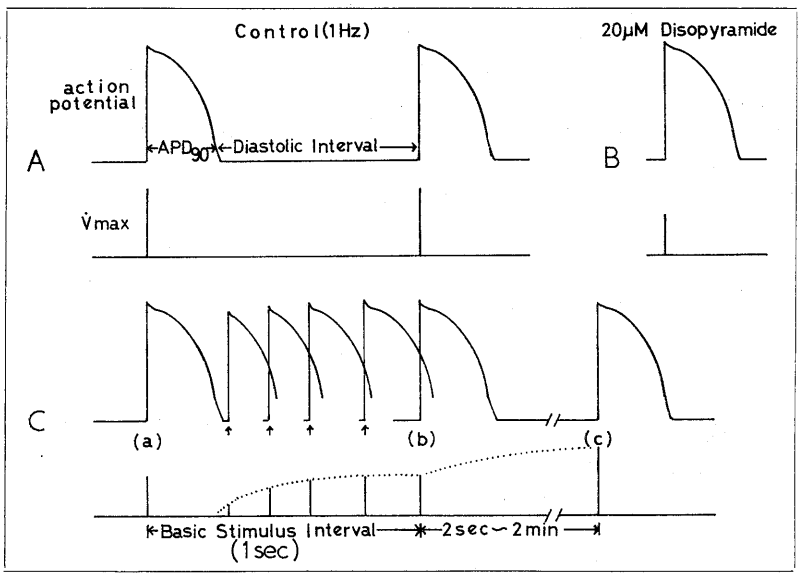

Fig. 1 Schematic representation of cardiac action potential and maximum upstroke velocity, $\dot{V}_{max}$, (A), effects of 20 μM disopyramide on $\dot{V}_{max}$ at 1 Hz (B) and the recovery process of $\dot{V}_{max}$ during diastolic interval (C). The recovery process was divided into two parts, premature recovery ((a)–(b)) and post-interruption recovery ((b)–(c)). Premature action potentials were elicited by premature test stimuli (indicated by arrows) interposed into various stages during diastole at 1 Hz. Note that between (b) and (c), the values of $\dot{V}_{max}$ that had been reduced in the presence of the drug was restored as the interruption-period increased, and that it reached the steady value close to that in control. The dotted-line in C denoted the envelopes of $\dot{V}_{max}$ throughout the whole recovery course.

and recording transmembrane potentials have been previously described[3]. In brief, the papillary muscle dissected from the right ventricle of guinea-pig (300-500 g) was mounted in a 3 ml-recording chamber and superfused at a flow rate of 3-5 ml/min with a gassed (95% O_2+5% CO_2) Tyrode solution (36.5±0.5°C, pH 7.3-7.4) of the following composition (mM) : NaCl, 136.9; KCl, 5.4; $CaCl_2$, 1.8; $MgCl_2$, 1.05; NaH_2PO_4, 0.42; $NaHCO_3$, 11.9; glucose, 10.0. The action potential was measured using a 3 M KCl-filled microelectrode (resistance, 8-20 M ohm), and its first time derivatives ($\dot{V}_{max}$) was obtained by an electronic differentiator (time constant: 50 μsec). The muscle was driven electrically with rectangular pulses (0.5-3.0 V, 1 msec duration, 1.1-1.4 times threshold).

Maximum upstroke velocity ($\dot{V}_{max}$) and action potential duration at 90% repolarizing level (APD 90) were measured as action potential parameters (Fig. 1 A). The recovery process of V_{max} during diastole was detected as follows (Fig. 1 C): i) The process within the basic stumulation interval of 1 sec (premature recovery) was studied by measuring $\dot{V}_{max}$ of premature action potential responded to premature stimuli. ii) The process beyond the basic stumulation interval (post- interruption recovery) was studied by assessing the $\dot{V}_{max}$ in the first response after interruption of the basic stimuli for various periods (2 sec to 2 min). The term "diastolic interval" is defined as the interval from the 90% repolarizing time of the conditioning action potential to the onset of the test action potential.

Drug

The disopyramide base was dissoled in adequate amounts of 0.2 N HCl and then neutralized to pH 7.0 by adding 0.5 N NaOH solution. The disopyramide concentration of 20 μM was chosen because therapeutically effective plasma concentrations of the drug was reported to be 1-8 μg/l (3-24 μM)[6].

Results

The most prominent action of 20 μM disopyramide on cardiac electrical activities was a reduction of the maximum upstroke velocity ($\dot{V}_{max}$) of action potential (Fig. 1 B). The effect on $\dot{V}_{max}$ reached a steady-state level within 60 min after an introduction of the drug. $\dot{V}_{max}$ was reduced by continuous stimulation at 1 Hz in the presence of the drug whereas it was restored in magnitude as the diastolic interval became longer (Fig. 1C).

Fig. 2 shows the premature recovery (at a diastolic interval less than 1 sec) and post-interruption recovery before and after the drug superfusion with 2.7, 5.4 and 8.1mM $[K^+]_0$. The $\dot{V}_{max}$ values were reduced by repetitive stimulation at 1 Hz in the presence of the drug. However, the values recovered toward those before introducing the drug as the diastolic interval was prolonged (Fig. 2 also Fig. 1C). In the presence of the drug, percentages of $\dot{V}_{max}$ at a diastolic invalter of 100 msec (premature recovery) were 84.2±2.7, 80.5±2.0 and 74.0±3.0% of the control values measured at the same diastolic interval in 2.7, 5.4 and 8.1 mM $[K^+]_0$, respectively. This implies that premature recovery process in the high $[K^+]_0$ is so slow that the reactivation of Na inward current system at these short diastolic intervals was incomplete. In contrast, percentages of $\dot{V}_{max}$ at the longest interruption periods of 2 min (post-interruption recovery) were 87.1±2.3, 90.0±1.8 and 99.5±1.0% of the control values in 2.7, 5.4 and 8.1 mM $[K^+]_0$, respectively. That is, in high $[K^+]_0$ $\dot{V}_{max}$ that was reduced by repetitive stimulation at 1 Hz in the presence of the drug was completely restored and reached the value close to that before the drug. However, in low $[K^+]_0$, the recovery slowed, so that $\dot{V}_{max}$ at a diastolic interval of 2 min was still less than that in control. These results indicate that the elevation of $[K^+]_0$ from 2.7 to 8.1 mM slowed the premature recovery of $\dot{V}_{max}$, but accelatated the post interruption recovery of $\dot{V}_{max}$.

The whole recovery process, which included both the premature- and postinterruption recovery was found to be approximated by a sum of three exponential func-

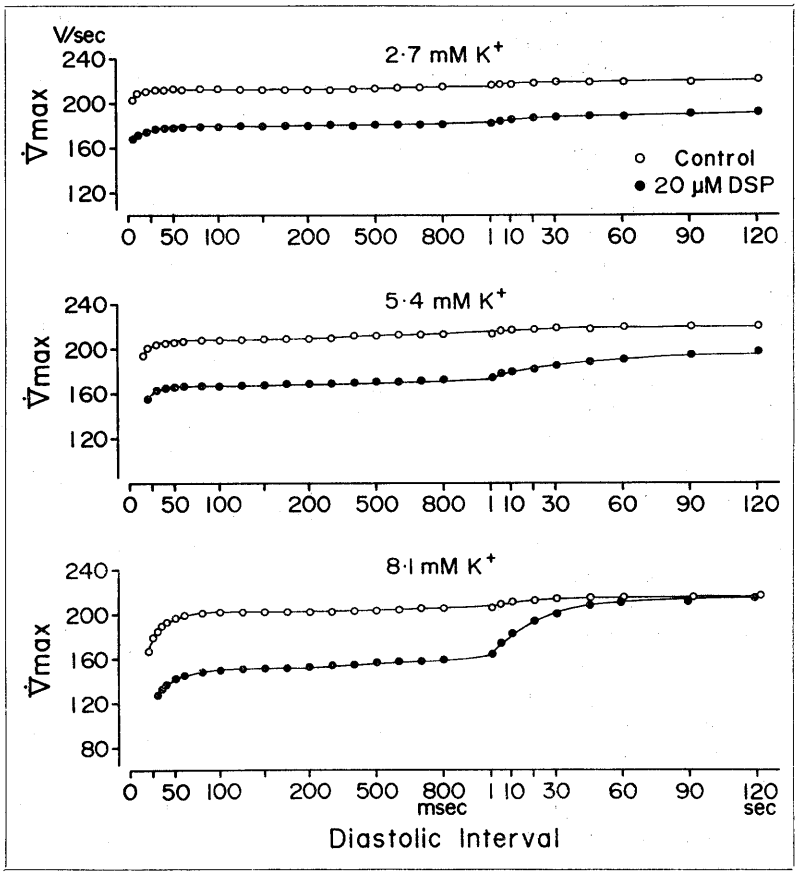

Fig. 2 The recovery process of $\dot{V}_{max}$ in the absence and presence of disopyramide (DSP) in 2.7, 5.4 and 8.1 mM $[K^+]_0$. In each $[K^+]_0$ level, records were obtained from a continuous impalement of a single cell during both control and drug superfusion periods. Data were expressed as mean values (S.E. were not shown): n=4 in 2.7 and 5.4 mM $[K^+]_0$ and n=5 in 8.1 mM $[K^+]_0$. The lines were drawn using the parameters given in Table 1.

Table 1 Influence of K^+ Concentration on the Speed (time constant) of the Three Components of the Recovery Process in the Presence of Disopyramide, 20 μM

$[K^+]_0$	Earliest (msec)	Intermediate (sec)	Latest (sec)
2.7 mM (n=4)	14 msec	0.98 sec	65 sec
5.4 mM (n=4)	12 msec	0.75 sec	50 sec
8.1 mM (n=5)	20 msec	0.80 sec	23 sec

tions, earliest, intermediate and lastest components. A detailed procedure to distinguish each exponential function from the whole recovery course was described elsewhere[5]. Table 1 shows the influence of external potassium concentration, $[K^+]_0$, on the recovery process of each component. From the table, it was evident that high $[K^+]_0$ slowed the recovery of the earliest component in the presence of the drug and accelerated that of the latest component, and that low $[K^+]_0$ slowed that of the latest one.

Discussion

From the findings described above, it may be concluded that disopyramide modified $\dot{V}_{max}$ in $[K^+]_o$- and time-dependent fashions. The present study also demonstrated that when $[K^+]_o$ was elevated from 2.7 to 8.1 mM, disopyramide slightly slowed the process of premature recovery of $\dot{V}_{max}$, but markedly accelerate the post-interruption recovery time course. The $[K^+]_o$-dependent action suggests that the effects of the drug on the Na^+ inward current system is voltage-dependent, because the membrane potential is known to change when $[K^+]_o$ is changed. With respect to the time-dependent property of the effect of the drug on Na^+ current system, the analysis for the recovery process showed that the whole recovery time course was fitted by the sum of three exponential functions and that disopyramide slowed them separately. The finding on the time- and voltage-dependence implies that disopyramide may suppress more preferentially the fast Na^+ inward current of high frequency impulses in depolarized tissue (high $[K^+]_o$) and that of extremely low frequency impulses in hyperpolarized tissues (low $[K^+]_o$). Such preferrential blocking action of disopyramide was reported in guinea-pig atrial preparation[7].

In view of the reports that lidocaine increased but quinidine and procainamide did not changed the time constant of the recovery process of $\dot{V}_{max}$ in high $[K^+]_o$[4,5,8], the above action of disopyramide is considered to be unique and has never been reported for any other antiarrhythmic drugs. However, such retardation of the recovery process of Na^+ current system in high $[K^+]_o$ was evident only at extremely long diastolic itervals as compared with physiological heart rates (the time constant for this component: several ten secs), this action may not be operative in the clinical situation. Actually, disopyramide has been claimed not to be effective against arrhythmias in hypopotassemia[9,10].

In summary, the more depressant action of disopyramide on $\dot{V}_{max}$ was demonstrated at short diastolic intervals in high $[K^+]_o$, or at long diastolic intervals in a low $[K^+]_o$. Since the depression of fast Na^+ inward current system in the re-entry arrhythmias is thought to be advantageous because of an alteration of unidirectional block to bidirectional one, it was concluded that disopyramide may block early extrasystole and tachycardia selectively in the depolarized tissues.

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