

ELECTROPHYSIOLOGICAL EFFECTS OF IMPRAMINE ON BOVINE VENTRICULAR MUSCLE AND PURKINJE FIBRES

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- 1 The effect of imipramine in concentrations between 0.01 μM and 50 μM has been studied on bovine Purkinje fibres and ventricular muscle transmembrane potentials.
- 2 In electrically stimulated fibres, imipramine had no effect on the resting membrane potential, but decreased the action potential amplitude, overshoot and maximum rate of depolarization (\dot{V}_{max}).
- 3 In Purkinje fibres, imipramine also decreased the conduction velocity and shifted the membrane responsiveness and recovery time curves downward and to the right.
- 4 In both Purkinje fibres and ventricular muscle, imipramine decreased the amplitude of phase 2 and prolonged phase 3. In Purkinje fibres, imipramine did not alter the action potential duration (APD) but prolonged the effective refractory period (ERP). In ventricular muscle, at concentrations higher than 1 μM imipramine shortened both the APD and the ERP and made the ERP long as compared to APD.
- 5 Imipramine decreased the slope of phase 4 diastolic depolarization in spontaneously beating Purkinje fibres.
- 6 These properties of imipramine are quite similar to those of quinidine or procainamide (class 1 antiarrhythmics). The mechanisms responsible for the cardiac effect of imipramine are discussed.

Introduction

Tricyclic antidepressants have powerful effects on the cardiovascular system. Soon after the introduction of imipramine, Kristiansen (1961) reported minor ST-T changes in the electrocardiogram and hypotension of treated patients. Since then, various changes in the ECG-pattern, including prolongation of the PQ and QT intervals, ST and T-wave abnormalities and widening of the QRS complex, have been described both after overdosage or during chronic therapy (Jefferson, 1975). Most clinical reports also claim that imipramine may produce ventricular arrhythmias in patients with or without antecedent heart disease (Vohra, Burrows & Sloman, 1975). On the other hand, some experimental (Sigg, Osborn & Korol, 1963; Fekete & Borsy, 1964) and clinical reports (Bigger, Giardina, Kantor & Glassman, 1977) indicate that imipramine could act as an antiarrhythmic agent. Recent studies in guinea-pig papillary muscles (Garcia de Jalón, Rodriguez & Tamargo, 1978) have demonstrated that it decreased the maximum rate of depolarization, shortened the action potential duration and suppressed the calcium-mediated action potentials. However, little information is available on the effects of imipramine on Purkinje fibres. The present study was undertaken to evaluate the electrophysiological properties of this drug on bovine isolated Purkinje fibres and ventricular muscle.

Methods

Preparations containing Purkinje fibres and ventricular muscle were dissected at the local slaughterhouse and pinned to the waxed floor of a 3 ml Lucite chamber. The chamber was perfused with Tyrode solution gassed with 95% O₂ and 5% CO₂, at a constant rate of 7 ml/min; the temperature of the perfusate was maintained at 37°C. The composition of the Tyrode solution (mmol/l) was: NaCl 137, KCl 5.4, CaCl₂ 1.8, NaH₂PO₄ 0.2, NaHCO₃ 12 and dextrose 5.5. The preparations were initially driven at a basal frequency of 1 Hz and a period of 1 h was allowed for equilibration while a stable impalement was established. After the equilibration the frequency was varied between 0.3 and 2 Hz. Frequencies of stimulation were changed stepwise and the records were taken 30 s after each change in rate. Driving stimuli were rectangular pulses (1 to 2 ms duration and 1.5 times diastolic threshold) delivered to the preparation from a programmable multi-purpose stimulator. Electrical stimulation was applied to the surface of the preparation through Teflon-coated bipolar electrodes of silver wire.

Transmembrane action potentials were recorded with glass microelectrodes filled with 3 M KCl. Electrode resistance ranged from 10 to 30 megohms. The microelectrode was coupled with an Ag-AgCl bar which led into high input impedance and input ca-

capacity neutralization amplifiers. The outputs of the amplifiers were displayed on a Tektronix 5103N storage oscilloscope. The oscilloscope traces were photographed with a Grass C4 Kymograph camera.

The following action potential characteristics were evaluated: action potential amplitude; overshoot; maximum rate of rise; resting potential; action potential duration at 50% (APD₅₀) and 90% (APD₉₀) repolarization; effective refractory period (ERP); recovery time; membrane responsiveness and conduction velocity. The maximum rate of rise of phase 0 depolarization (\dot{V}_{max}) of the action potential was obtained by a differentiator with a linear output between 100 and 1000 V/s. The relationship between \dot{V}_{max} and membrane potential, i.e. membrane responsiveness, was measured by stimulation in different external K concentrations (between 2.7 and 10.8 mM; Carmeliet, Xhonneux, Van Glabbeek & Reneman, 1976). The ERP, defined as the period in which no propagated action potential can be obtained, and the recovery time, defined as the time needed for the \dot{V}_{max} of the upstroke to recover its full amplitude, were determined by delivering premature test-stimuli of twice threshold strength at various intervals from the preceding driving stimulus. The interpolation and shift along the time axis were carried out automatically every eighth basic drive stimulus. The conduction time in Purkinje fibres was measured between two intracellular microelectrodes and the conduction velocity was then calculated. Pacemaker activity was tested in Purkinje fibres bathed in 2.7 mM K Tyrode; in ventricular muscle spontaneous activity was induced by adding 0.2 mM BaCl₂ to the normal perfusion solution.

Imipramine, as a powder, was initially dissolved in deionized distilled water. Further dilutions were carried out in Tyrode solution to obtain final concentrations between 0.01 μ M (0.0028 μ g/ml) and 50 μ M (14.0 μ g/ml).

All values are expressed as mean \pm s.e. and the significance of differences has been estimated by Student's *t* test or Student's paired *t* test. A *P* value of <0.05 was considered statistically significant.

Results

Effect of imipramine on action potential characteristics

The effect of imipramine in concentrations between 0.01 μ M and 50 μ M was studied in Purkinje fibres and ventricular muscle. The effects of the drug were usually evident within 5 min after the beginning of the perfusion and stabilized within 25 to 30 min. The electrophysiological changes induced by concentrations up to 1 μ M were completely reversed within 40 to 60 min of perfusion with drug-free Tyrode solution. When higher concentrations of imipramine were used the changes were only partly reversible or irreversible.

Purkinje fibres. The effects of imipramine, 0.01 μ M to 50 μ M, on action potential characteristics were studied in Purkinje fibres. Control values of the measured parameters and results obtained after 30 min exposure to imipramine at different concentrations are shown in Table 1. The data obtained with concentrations up to 1 μ M on action potential amplitude, overshoot and \dot{V}_{max} were omitted from this table because they were not statistically different from controls. Higher concentrations of imipramine produced a concentration-dependent decrease in these three parameters without having any effect on membrane resting potential. In addition to the depression of peak \dot{V}_{max} , imipramine produced a time-dependent change on \dot{V}_{max} in Purkinje fibres. The effects of imipramine on Purkinje \dot{V}_{max} were examined over a wide

Table 1 Electrophysiological effects of imipramine on bovine Purkinje fibres

	Resting potential (mV)	Overshoot (mV)	Amplitude (mV)	dV/dt (V/s)	APD ₅₀ (ms)	APD ₉₀ (ms)
Control (14)	88.8 \pm 2.3	30.1 \pm 2.0	119.3 \pm 1.9	508.5 \pm 38.1	328.9 \pm 13.6	410.6 \pm 19.3
Imipramine 1 μ M	88.8 \pm 2.3	19.6 \pm 5.1**	108.6 \pm 6.0*	465.3 \pm 33.2*	302.8 \pm 11.2*	405.6 \pm 19.0
Control (12)	88.6 \pm 1.5	29.1 \pm 2.4	118.2 \pm 1.7	486.5 \pm 30.7	336.2 \pm 10.3	419.3 \pm 17.3
Imipramine 5 μ M	88.3 \pm 1.2	16.2 \pm 2.0***	104.0 \pm 2.6**	381.5 \pm 24.6**	301.0 \pm 12.6*	410.0 \pm 16.6
Control (12)	87.8 \pm 1.3	29.6 \pm 3.4	118.0 \pm 2.1	505.2 \pm 32.8	333.6 \pm 10.2	416.0 \pm 19.8
Imipramine 10 μ M	86.7 \pm 1.5	15.0 \pm 2.0***	100.5 \pm 2.9***	360.9 \pm 41.6***	302.3 \pm 13.7*	409.3 \pm 16.3

Values are mean \pm s.e. mean. Number of observations (*n*) in parentheses. Readings started after 30 min of perfusion with imipramine. APD₅₀ and APD₉₀ refer to action potential duration measured to 50% and 90% repolarization, respectively.

* *P* < 0.05; ** *P* < 0.01; *** *P* < 0.001.

range of frequencies. The results of seven experiments are shown in Figure 2a. Before treatment the control Purkinje \dot{V}_{max} was slightly depressed at the two most rapid frequencies of stimulation. Imipramine (1 μM , 5 μM and 10 μM) significantly ($P < 0.01$) reduced the peak \dot{V}_{max} at any given frequency, but the decrease was less pronounced the lower the frequencies. A similar rate-dependence of \dot{V}_{max} was observed when instead of constant rates of stimulation, premature action potentials were elicited at different intervals after the end of the preceding basic action potential. When the fibres were exposed to the highest concentration of imipramine (50 μM) there was a marked decrease in \dot{V}_{max} accompanied by a depression of the rapid component of the upstroke. In fact, shortly after exposure to this concentration, the upstroke consisted of two phases, a first phase markedly reduce in rate and amplitude, followed by a slow rising secondary depolarization up to the normal plateau level (Figure 1). At 50 μM all fibres became unexcitable in 10 to 15 min. The voltage-time course of the action potential was also altered by imipramine, shortening the APD_{50} . This shortening was mainly due to a depression in the amplitude of phase 2 and to an altered slope of the plateau which was shifted to more negative potentials. As a consequence, the onset of phase 3 occurred earlier and its duration progressively increased. However, the terminal portion of phase 3 repolarization was prolonged so that even though there was proportionately faster repolarization during earlier phases, the APD_{90} did not differ significantly from controls at any concentration (Table 1). The voltage-time course of repolarization of Purkinje fibres and a typical experiment is illustrated in Figure 1.

Ventricular muscle. The effects of imipramine were also studied in ventricular muscle. Table 2 summar-

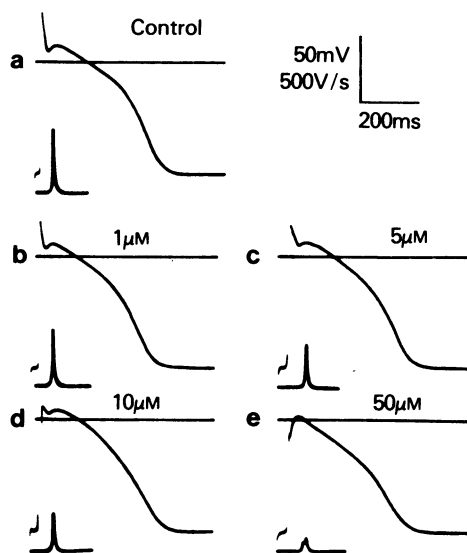


Figure 1 Effect of imipramine on action potential characteristics in bovine Purkinje fibres. In each panel the upper trace represents the zero potential base line and the bottom trace the differentiated upstroke of phase 0 (\dot{V}_{max}). The centre trace records the Purkinje fibre transmembrane potential. (a) Control, (b, c, d and e) obtained 30 min after beginning the perfusion with different concentrations of imipramine (1 μM , 5 μM , 10 μM and 50 μM , respectively).

izes the data and Figure 3 shows a typical experiment. Imipramine at concentrations higher than 5 μM caused a progressive decrease in action potential amplitude, overshoot and \dot{V}_{max} , but no significant changes were observed at these concentrations in membrane resting potential. As in Purkinje fibres, imipramine decreased the \dot{V}_{max} in ventricular fibres at

Table 2 Electrophysiological effects of imipramine on bovine ventricular muscle

	Resting potential (mV)	Overshoot (mV)	Amplitude (mV)	dV/dt (V/s)	APD_{50} (ms)	APD_{90} (ms)
Control (12)	89.7 \pm 1.7	30.4 \pm 2.0	121.0 \pm 1.1	291.2 \pm 29.2	297.8 \pm 13.9	348.0 \pm 15.6
Imipramine 5 μM	89.4 \pm 1.9	20.1 \pm 2.2***	110.7 \pm 3.5*	255.3 \pm 18.1*	292.8 \pm 12.1	342.9 \pm 16.7
Control (10)	89.1 \pm 1.7	30.8 \pm 1.9	120.1 \pm 1.4	298.8 \pm 25.5	292.1 \pm 13.9	346.9 \pm 14.2
Imipramine 10 μM	89.0 \pm 2.0	15.3 \pm 2.2***	103.3 \pm 4.4***	204.6 \pm 30.8**	243.7 \pm 10.2**	321.6 \pm 11.2*
Control (12)	88.6 \pm 1.8	30.2 \pm 2.6	119.7 \pm 1.3	276.3 \pm 36.3	300.9 \pm 17.6	356.0 \pm 16.2
Imipramine 50 μM	88.2 \pm 1.3	-7.1 \pm 2.9***	85.2 \pm 3.8***	134.1 \pm 50.4***	246.4 \pm 21.4**	282.5 \pm 19.8**

Values are mean \pm s.e. mean. Number of observations (n) in parentheses. Readings started after 30 min of perfusion with imipramine. APD_{50} and APD_{90} refer to action potential duration measured to 50% and 90% repolarization respectively.

* $P < 0.05$; ** $P < 0.01$; *** $P < 0.001$.

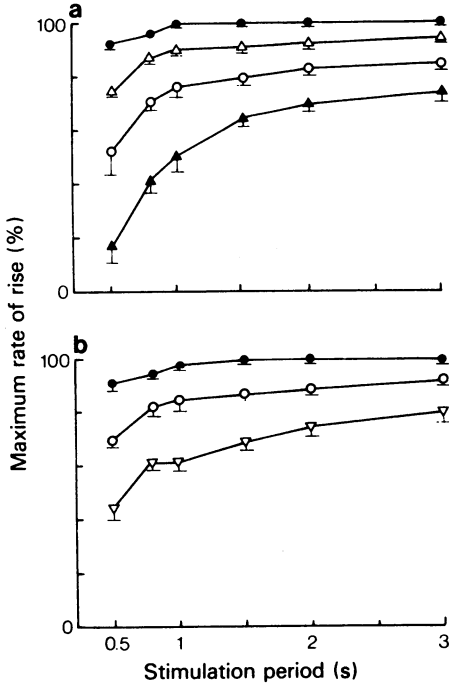


Figure 2 Effect of imipramine on the maximum rate of depolarization at various frequencies of stimulation in Purkinje fibres (a) and ventricular muscle (b). The maximum rate of depolarization, expressed as percentage of the maximum rate of rise is plotted on the ordinate scale and the stimulation period in seconds on the abscissa scale. Observations are shown for control conditions (●) and after 30 min exposure to different concentrations of imipramine: (Δ) 1 μM, (○) 5 μM, (▲) 10 μM, (▽) 50 μM. Each point represents the mean of seven experiments; vertical bars represent s.e. mean.

all stimulation frequencies, but the decrease was greater at rapid than at low frequencies (Figure 2b). At these concentrations (10 μM and 50 μM), imipramine significantly shortened the APD_{50} and APD_{90} ($P < 0.01$). This shortening was due to an increased slope of phases 2 and 3. At 50 μM the inflection between phases 2 and 3 became less distinct and the action potential presented a triangular configuration. The shortening in APD was dependent on the frequency of stimulation and was more pronounced at lower frequencies where the APD was longer. However, the percentage change in APD was almost identical at all frequencies of stimulation.

Membrane responsiveness and recovery time

To examine further the action of imipramine on \dot{V}_{max} in Purkinje fibres, the effects of the drug were examined in eight experiments on the relationship between the \dot{V}_{max} and the membrane potential at the onset of depolarization, i.e. membrane responsiveness. Electrical activity was recorded during a step-wise increase of the external potassium concentration (2.7 to 10.8 mM). Concentrations of imipramine higher than 1 μM produced a concentration-dependent decrease in peak \dot{V}_{max} and shifted the membrane responsiveness curve downwards and to the right (Figure 4). At these concentrations there was a progressive shift in the values of V_h (the membrane potential at which \dot{V}_{max} is reduced to half of its maximum value) to more negative potentials. In Figure 4 the V_h value under control conditions was -72 mV and those following the exposure to 5 μM and 10 μM were -75 mV and -82 mV, respectively.

Recovery time, i.e. the time needed for the \dot{V}_{max} and the amplitude of the action potential to recover its full

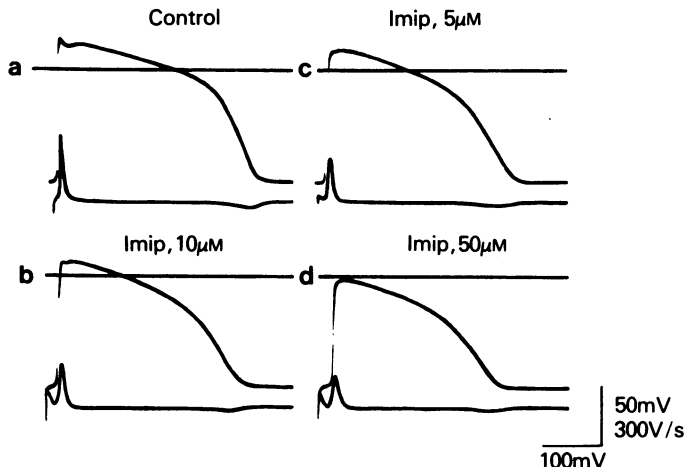


Figure 3 Effects of imipramine (Imip) on action potential characteristics in bovine ventricular muscle fibres. The centre trace records the ventricular muscle transmembrane potential. (a) Control, (b, c and d) were obtained after 30 min perfusion with imipramine (5 μM, 10 μM and 50 μM, respectively).

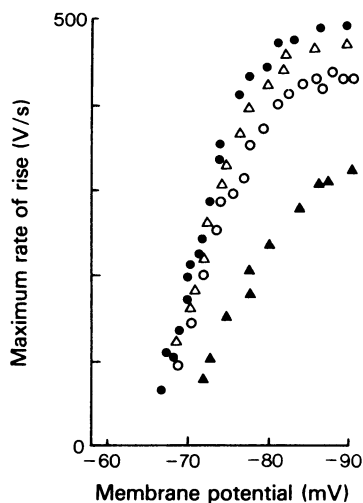


Figure 4 Effects of imipramine on the membrane responsiveness curve in bovine Purkinje fibres. The maximum rate of depolarization (V/s) is plotted on the ordinate scale and the membrane potential at the time of activation (in mV) on the abscissa scale. (●) Control; imipramine (Δ) 1 μM; (○) 5 μM; (▲) 10 μM. All perfusion periods, 30 min.

amplitude, was studied in five experiments. Imipramine, 1 μM and 10 μM, depressed the recovery time, shifting the curve downwards and to the right (Figure 5). As can be observed in this figure, at these concentrations imipramine also prolonged the ERP in Purkinje fibres and reduced the \dot{V}_{max} of the first premature response.

Conduction velocity

The decrease in action potential amplitude and \dot{V}_{max} resulted in a fall of the conduction velocity. Conduction time was measured between two intracellular microelectrodes located at either end of a free-running Purkinje fibre. The action potential recorded from the two sites were displayed at fast sweep speed allowing the measurement of conduction time between the two action potential upstrokes. The distance between the two microelectrodes was estimated through the micrometer eye piece of the microscope. In five experiments exposure to imipramine (1 μM, 5 μM and 10 μM) for 30 min, decreased the control conduction velocity (2.8 ± 0.6 m/s, mean \pm s.e.) to 2.2 ± 0.4 m/s, 1.8 ± 0.3 m/s and 1.4 ± 0.2 m/s, respectively ($P < 0.01$). These effects were still more pronounced at higher frequencies of stimulation. In Purkinje-muscle preparations, a partial block in orthodromic direction was observed after perfusion with imipramine, 10 μM.

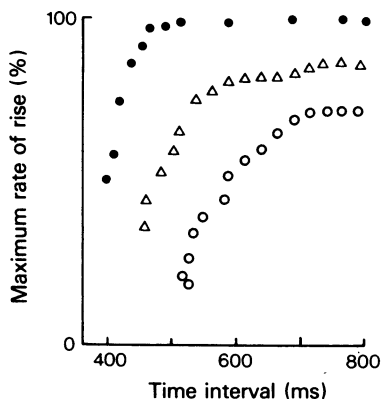


Figure 5 Effects of imipramine on the recovery time curve in bovine Purkinje fibres. The maximum rate of depolarization of premature responses expressed as percentage of the maximum rate of rise in the control solution is plotted on the ordinate scale and the interval between basic driving stimuli and test stimuli on the abscissa scale. (●) Control; imipramine (Δ) 1 μM, (○) 10 μM. All perfusion periods, 30 min.

Effective refractory period

The ERP, defined as the period in which no propagated action potentials can be obtained, was determined in Purkinje fibres and in ventricular muscle in eight experiments. Preparations were driven at a constant rate and premature test-stimuli were delivered at various intervals every eighth basic drive stimulus. In Figure 6 the changes in the ERP and in action potential duration in Purkinje and ventricular fibres expressed as percentage change are plotted as a function of imipramine concentrations. Concentrations up to 1 μM exerted no significant effects on the ERP in both fibre types. Higher concentrations of imipramine progressively prolonged the ERP in Purkinje fibres and because the duration of the action potential was not significantly altered at any concentration, exposure to concentrations higher than 1 μM prolonged the ERP in absolute value. In ventricular muscle, concentrations above 1 μM shortened significantly the duration of the action potential and the ERP. The mean ERP reached a minimum at concentrations of 5 μM. In these fibres the ERP-concentration curve differed significantly from the action potential duration-concentration curve in that the ERP-concentration curve had an ascendent limb (Figure 6). However, the ERP remained significantly shorter than control until a 50 μM concentration was used; at this concentration the value of the ERP was significantly different from control ($P < 0.05$).

Therefore, at concentrations of imipramine above 1 μM the changes induced in the ERP in Purkinje fibres and in ventricular muscle were always greater than

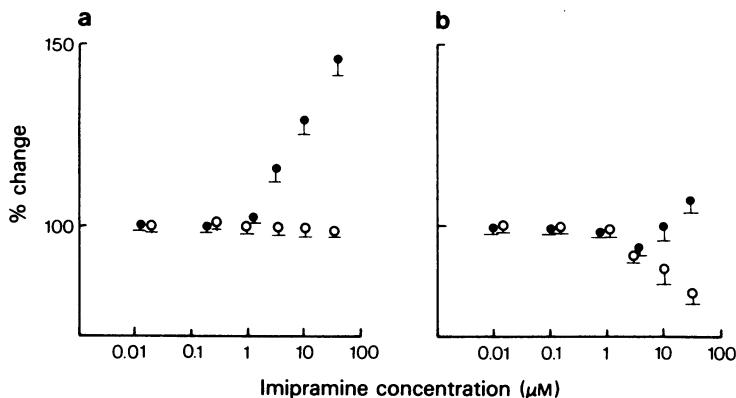


Figure 6 Changes in the effective refractory period (ERP) and in action potential duration (APD) of Purkinje fibres (a) and ventricular muscle (b) as a function of imipramine concentration in the perfusate. ERP (●) and APD (○) are plotted on the ordinate scale as percentage change and the concentration of imipramine (μM) on the abscissa scale. Each point represents the mean of eight experiments; vertical bars represent s.e. mean.

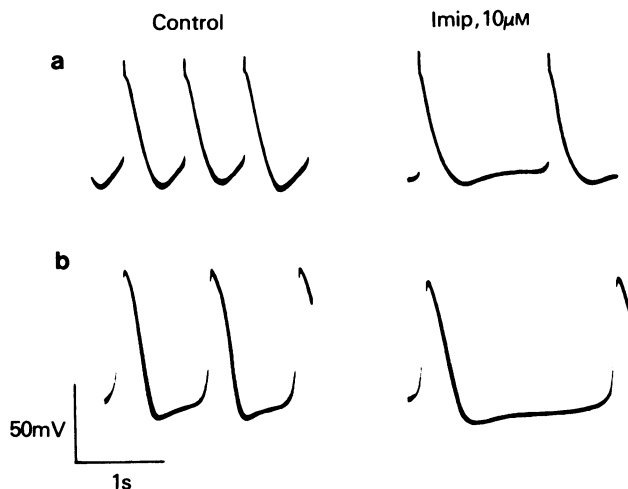


Figure 7 Effect of imipramine on automaticity in bovine Purkinje fibres and ventricular muscle. Panel (a) left, shows spontaneous automaticity induced in Purkinje fibres perfused in Tyrode solution containing 2.7 mM external potassium. Panel (b) left shows automatic activity induced in ventricular muscle fibres perfused with Tyrode solution containing 0.2 mM BaCl_2 . Addition of imipramine (Imip 10 μM) for 30 min to the perfusate results in a decrease of the rate of diastolic depolarization in both Purkinje (panel a, right) and ventricular (panel b, right) fibres.

the changes induced in APD, so that the ratio of the change in ERP to the change in APD was always greater than one.

Spontaneous activity

The effects of imipramine were examined in seven spontaneously beating Purkinje fibres in which automaticity was elicited by reducing the external potassium concentration to 2.7 mM. A typical experiment is shown in Figure 7a. In all preparations imipramine (5

μM) significantly reduced the slope of phase 4 diastolic depolarization and slowed the spontaneous rate. This effect was largely due to a selective decrease in the rate of diastolic depolarization during late diastole, whereas it affected phase 4 only slightly during early diastole. At a concentration of 10 μM , imipramine suppressed the spontaneous activity with the membrane potential arrested at a depolarized level (Figure 7a, right). Similar results were obtained in four other experiments in which automatic activity was induced in ventricular muscle bathed in Tyrode

solution containing 0.2 mM BaCl₂ (Figure 7b). Imipramine (10 μM) again effectively suppressed the increase in automaticity induced by Ba ions in ventricular muscle fibres (Figure 7b, right).

Discussion

Transmembrane potentials of Purkinje fibres and ventricular muscle were studied during perfusion with imipramine. The concentrations used in this study, ranging from 0.0028 μg/ml to 14 μg/ml, comprised both therapeutic plasma levels (95 to 1050 ng/ml) and those found after over-dosage (up to 2190 ng/ml; Glassman & Perel, 1973). However, it is very difficult to relate *in vivo* plasma concentrations to the concentrations of the drug perfusing isolated cardiac tissues, particularly when a 10 to 20 fold variation in tricyclic plasma levels has been found among patients taking the same dose (Asberg, 1973; Glassman & Perel, 1973). On the other hand, it is known that some therapeutic or toxic effects of imipramine appeared only after repeated administration of the drug for days or weeks.

Imipramine decreased action potential amplitude, overshoot and \dot{V}_{max} in the absence of any change in resting membrane potential, depressed membrane responsiveness and slowed ventricular conduction. These effects were similar to those described for antiarrhythmic drugs having local anaesthetic properties on nerve, i.e. quinidine or procainamide, and have been attributed to an interference with an increase in Na conductance (gNa) and as a consequence, with the activation of the fast inward Na⁺ current during phase 0 depolarization (Weidmann, 1955b; Vaughan Williams, 1970). In fact, imipramine appears to be 2.7 and 6.7 times more potent as a local anaesthetic than lidocaine and mepiramine, respectively, and 4 times as active as tetracaine on desheathed frog nerve (Guerrero & Molgo, 1974). Recently, in voltage-clamp experiments, imipramine (1 to 50 μM) was shown to suppress the gNa in the *Myxicola* giant axon without having any effect on resting membrane potential (Schauf, Davis & Kesler, 1975). Action potential amplitude and \dot{V}_{max} are important determinants of conduction velocity (Hoffman & Cranefield, 1960). Thus, the decrease in gNa partially explains the slowed conduction observed during imipramine perfusion. Imipramine also depressed the \dot{V}_{max} at all levels of membrane potential and in Purkinje fibres shifted the membrane responsiveness curve along the voltage axis to more negative membrane potentials, which indicates that the drug largely inactivated most of the Na⁺-carrying system at relatively high membrane potentials (Weidmann, 1955a). Because of reduced responsiveness, repolarization has to proceed to more negative values before re-excitation can

occur, resulting in a prolongation of refractoriness independent of any change in APD (Vaughan Williams, 1958).

The effects of imipramine on \dot{V}_{max} were dependent on the frequency of stimulation. The same phenomenon has been described for quinidine (Johnson & McKinnon, 1957), as well as for phenothiazines (Arita & Surawicz, 1973) and desipramine (Tamargo, Rodriguez & Garcia de Jalon, 1979). Three mechanisms could explain the imipramine-induced time-dependence of \dot{V}_{max} : (a) an increase in the time constant of reactivation of the Na⁺-carrying system. In the present experiments the recovery time, which demonstrated the process of recovery from inactivation (reactivation) of the gNa, was depressed in Purkinje fibres perfused with imipramine. A similar mechanism has been proposed to explain the quinidine-induced dependence of \dot{V}_{max} on time (Szekeres & Vaughan Williams, 1962; Liebswar, Thaler & Heistracher, 1970). (b) A persistent effect of outward current during the preceding plateau. This hypothesis could explain the decrease in \dot{V}_{max} observed in Purkinje fibres but it does not explain the effect observed in ventricular muscle, where this time-dependent outward current is very small (Giebisch & Weidmann, 1971). (c) An accumulation of intracellular Na⁺ due to inhibition of the Na⁺ extrusion process. It has been reported that imipramine inhibits the Na⁺-K⁺ATPase from the cortex of brain and kidney (Medzihradsky & Nandhasri, 1972); a similar effect on cardiac cell membrane might inhibit the Na⁺-pump activity and decrease Na⁺ extrusion. However, the electrophysiological effects of imipramine described here were obtained at lower concentrations than those necessary to inhibit the Na⁺-pump (50 μM).

In both Purkinje and ventricular fibres imipramine depressed the amplitude of the plateau, resetting its level to more negative membrane potentials and prolonged the duration of phase 3. In Purkje fibres the prolongation of phase 3 paralleled the progressive increase in the slope of phase 2, as indicated by the nearly constant APD. However, the extent to which imipramine might modify the ionic mechanisms responsible for the generation of the plateau in Purkinje fibres and ventricular muscle is a matter that requires further voltage-clamp studies.

Ventricular arrhythmias may result from abnormalities in impulse formation and/or conduction (Cranefield, Wit & Hoffman, 1973). Suppression of automaticity has been considered to be one of the essential electrophysiological properties of antiarrhythmic drugs. Imipramine could suppress automatic rhythms originating in the His-Purkinje system directly, since it greatly decreased the slope of phase 4 diastolic depolarization in spontaneously beating Purkinje fibres; moreover, it also depressed the

Ba-induced automaticity elicited in ventricular muscle. Weidmann (1955b) suggested that the principal mode of action of quinidine and procainamide is a prolongation of the ERP of Purkinje fibres out of proportion to any increase in APD. Since then, an increase of the ratio ERP over APD has been considered as an important requisite for antiarrhythmic effectiveness. Imipramine increased the ratio in both Purkinje fibres and ventricular muscle. Prolongation of the ERP in absolute value was observed in Purkinje fibres, while in ventricular muscle ERP was prolonged only in relation to a shorter action potential. Imipramine would thus cause early recirculating impulses to be blocked, and the rate of depolarization of the earliest premature beat will occur at more negative membrane potentials, thereby enhancing intraventricular conduction and possibly eliminating re-entrant beats by depressed conduction. Imipramine also decreased intraventricular conduction. A sufficient reduction in conduction velocity could interrupt ventricular re-entry by another mechanism, i.e. by transformation of unidirectional into bidirectional conduction block.

Most of the observed effects of imipramine on ventricular action potentials that already have been described are similar to the effects of compounds classified as membrane stabilizers, class 1 antiarrhythmics according to the classification of Vaughan Williams (1970). However, this study reveals that imipramine also decreased conduction velocity, increased the dis-

crepancy between the APD in the Purkinje fibres and in the ventricular muscle, and altered the relation between ERPs in the Purkinje and in the ventricular fibres. These effects decreased ventricular electrical stability by increasing the difference in dispersion of ventricular refractoriness and increased the non-uniform recovery of excitability between Purkinje fibres and ventricular muscle. On the other hand, depression of conduction may lead to adverse effects such as decremental conduction or block in previously normal cardiac tissues. As a consequence, imipramine increased ventricular inhomogeneity and enhanced the tendency to re-entry phenomena resulting in ventricular premature beats and ventricular tachycardia (proarrhythmic effects of imipramine). The intraventricular conduction disturbances observed in patients treated with imipramine may be attributed to a combination of a decrease in membrane responsiveness and to the induction of time-dependent changes in the \dot{V}_{max} of Purkinje and ventricular fibres. Reduction of \dot{V}_{max} and conduction velocity could also explain the widening of the QRS complex, and since the changes were more pronounced at rapid heart frequencies they could explain the ventricular aberrancy accompanying tachycardia in treated patients. Slowing of the terminal portion of repolarization in Purkinje fibres may be responsible for the decrease in T wave amplitude and possibly for the ST-T abnormalities and for the prolongation of the QTc interval observed in these patients.

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(Received July 3, 1979.)

Revised November 22, 1979.)