Effects of Tetrodotoxin, Lidocaine, Verapamil, and AHR-2666 on Ouabain-Induced Delayed Afterdepolarizations in Canine Purkinje Fibers

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SUMMARY. We used standard microelectrode techniques to record delayed afterdepolarizations (DAD) induced by ouabain (2 x 10^-7 m) in isolated canine Purkinje fibers (PF) and studied the response of DAD to the fast Na+ channel blocker, tetrodotoxin (TTX, 1 mg/liter); the slow channel blocker, verapamil (verap, 1 mg/liter); the putative Ca2+ blocker, AHR-2666 (AHR, 45 mg/liter); and lidocaine (lido, 4 mg/liter), which increases steady state outward current and decreases background inward current. PF were driven at cycle lengths of 1000-200 msec. Ouabain superfusion for 30 minutes induced DAD with amplitudes of 17.0 ± 1.5 (mean ± SE) mV at a cycle length of 200 msec. TTX, verap, and AHR, and lido all depressed DAD amplitude (P < 0.05). To intercompare the effects of the drugs, graphs were constructed relating DAD amplitude to basic cycle length, and the relative magnitude of effects of the drugs on DAD amplitude at all cycle lengths was tested using a nested analysis of variance. The effects of verap and AHR were equivalent, and both decreased DAD amplitude more at short (to 37% of ouabain control) than at long (to 76%) cycle lengths (P < 0.05). Lido had a different effect and decreased DAD nearly equivalently at short (to 64%) and long (to 75%) cycle lengths. The actions of TTX were intermediate between—and significantly different from—those of the other drugs (P < 0.05). AHR and verap appear to act similarly, by modifying the current responsible for DAD, whereas lido appears to act by a different mechanism, perhaps by increasing steady state outward current. The actions of TTX may be a result of its effect on the transient inward current or on a background current carried by Na+. Circ Res 46: 117-124, 1980

DELAYED afterdepolarizations are oscillations in membrane potential that can induce varying degrees of conduction block and/or paroxysmal impulse initiation (Cranefield, 1975). They occur in Purkinje (Davis, 1973; Ferrier et al., 1973; Rosen et al., 1973a, 1973b; Saunders et al., 1973) and atrial (Hashimoto and Moe, 1973; Hordof et al., 1978) specialized fibers after exposure to toxic concentrations of digitalis, and also in ventricular muscle (Ferrier, 1976). At the time of their occurrence in previously normal fibers, the transmembrane resting potential usually has decreased by approximately 10 mV. Delayed afterdepolarizations are induced by the action potential that precedes them, and both the coupling interval of the afterdepolarizations to the preceding action potential and their amplitude are dependent in part on the cycle length at which a preparation is driven. As cycle length decreases the afterdepolarization coupling interval also decreases, and the amplitude increases (Ferrier, 1973).

Several studies have attempted to determine the mechanisms responsible for delayed afterdepolarizations. Initially, experiments in which verapamil and manganese were used suggested that they were the result of an inward calcium current (Ferrier and Moe, 1973; Rosen et al., 1974). More recent voltage clamp studies (Lederer and Tsien, 1976; Aronson and Gelles, 1977) suggest that a transient inward current induces delayed afterdepolarizations. Lederer and Tsien hypothesized that, as the sodium pump is poisoned by digitalis, there is an intracellular accumulation of sodium, a reduced transmembrane concentration gradient for Na+, and a reduction in Ca2+ extrusion via the Na+-Ca2+ exchange. The latter, along with possible release of Ca2+ from mitochondria, is hypothesized too increase [Ca2+], which then triggers oscillatory movements of Ca2+ intracellularly. This in turn induces a conductance change for monovalent cations such as Na+, which may be a result of its effect on the transient inward current, the INa current (decay of which is responsible for normal automaticity in Purkinje fibers) is suppressed.

In preliminary experiments, Vassalle and Scida (1979) showed that TTX decreases the magnitude of digitalis-induced delayed afterdepolarizations. Their results suggest that the transient inward current responsible for delayed afterdepolarizations is carried by Na+ through a tetrodotoxin (TTX)-sensitive channel. Their results differ from those of...
Kass et al. (1978), who reported that delayed afterdepolarizations are not modified by TTX unless the preparation under study has been quiescent for a long (>20 minutes) time.

The purpose of the present study was to investigate the effects of the fast Na⁺ channel blocker, TTX; the slow channel blocker, verapamil; the putative Ca²⁺ blocker, AHR-2666 (Lustig and Kirsten, 1974; Siegel et al., 1975); and an agent that has been reported to increase steady state outward current, lidocaine (Weld and Bigger, 1976), on digitalis-induced delayed afterdepolarizations.

Methods

We anesthetized 20 adult mongrel dogs weighing 18-22 kg with Na pentobarbital, 30 mg/kg, iv. The hearts were excised through a left thoracotomy, and Purkinje fiber bundles were removed from right and left ventricles and placed in cold Tyrode's solution having the following composition (mM): NaCl, 137.0; NaHCO₃, 12.0; KCl, 4.0; NaH₂PO₄, 1.8; MgCl₂, 0.5; CaCl₂, 2.7; dextrose, 5.5. The Purkinje fiber bundles were mounted in a Lucite chamber and superfused with Tyrode's solution that was warmed to 37.5°C using a glass heat exchanger and gassed with 95% O₂, 5% CO₂. The preparations were impaled with 3 M KCl-filled glass capillary microelectrodes having tip diameters <1 μm and resistances of 10-30 MΩ. Only those experiments in which a continuous impalement was maintained throughout the drug superfusion period were included in the study. The methods used for stimulating the preparations and for recording action potential characteristics and the maximum rate of rise of the upstroke of the preceding action potential to the peak of the afterdepolarization; "2" indicates the interval for measuring delayed afterdepolarization amplitude. The first arrow indicates the MDP; the second the peak of the afterdepolarization. The difference between these two values is delayed afterdepolarization amplitude. Horizontal calibration, 600 msec; vertical, 20 mV.

For each experiment, the Purkinje fibers were driven at a basic cycle length of 500 msec. During control and at 5- to 10-minute intervals after the onset of superfusion with drugs, the fibers were stimulated at cycle lengths of 1000, 800, 600, 500, 400, and 200 msec, for 20 beats at each cycle length. Action potential characteristics for the last driven action potential in the train of 20 were measured. The drive stimulus was discontinued after driving at each cycle length to observe the occurrence of delayed afterdepolarizations and/or automaticity. In individual experiments, additional cycle lengths were studied as well.

After obtaining control records, the fibers were superfused with Tyrode's solution containing ouabain, 2 × 10⁻⁷ m, until delayed afterdepolarizations at least 5 mV in magnitude had occurred at a cycle length of 500 msec. This usually required 25-35 minutes. At this time, the stimulation protocol described above was repeated, and the ouabain was discontinued. The fibers then were superfused with one of the following test drugs: lidocaine, 4 mg/liter; TTX, 1 mg/liter; verapamil, 1 mg/liter; AHR-2666, 30, 45, and 60 mg/liter. Only results from AHR, 45 mg/liter, are reported here. The effects of this concentration were approximately equivalent to those of verapamil, 1 mg/liter. Overall, AHR, 30, 45, and 60 mg/liter, had a concentration-dependent effect, as has been reported previously (Siegel et al., 1975). The maximum effect of all of these drugs occurred in as little as 5 minutes (TTX) and at most 30 minutes (AHR-2666) after the onset of superfusion. At the time of maximum drug effect, we repeated the stimulation protocol.

We have shown in a previous study (Miura and Rosen, 1978) that, on discontinuation of superfusion of canine Purkinje fibers with ouabain, 2 × 10⁻⁷ m, its effects on the transmembrane potential are stable for 1 hour. Hence, any changes seen or any depression of the action potential or delayed afterdepolarizations occurring with the agents used in the present study can be assumed to be the result of the test drug effect rather than of ouabain wash-out. As an additional control, however, we did washout studies for lidocaine, 4 mg/liter; AHR-2666, 45 mg/liter; and TTX, 1 mg/liter (two experiments for each). All three drugs washed out within 30 minutes. Within this interval, delayed afterdepolarizations had occurred and were of approximately the same magnitude as those seen prior to discontinuing ouabain. We could not follow the same procedure for verapamil because an interval of 2 or more hours is required to reverse its effects; however, in light of the results with the other test drugs, we are confident that the actions we describe on delayed after-
Depolarizations are due to the drugs themselves rather than to significant washout of ouabain.

Data Analysis

The significance of differences in amplitude of delayed afterdepolarizations at various cycle lengths was studied using a one-way fixed effects analysis of variance (Snedecor and Cochran, 1967). Specification of which cycle lengths resulted in significant differences in delayed afterdepolarization amplitude was accomplished by t-tests of the groups in question, with protection of the α confidence maintained by Scheffe’s procedure. To test for differences in response of action potential duration and delayed afterdepolarization amplitude and upstroke velocity to the drugs studied, a nested (cycle length within test drug) analysis of variance was used. This procedure specifically tested for drug-related differences in the cycle length-delayed afterdepolarization amplitude curves. The unit for analysis was the individual fiber’s response. All statistical analyses were done on raw data.

For testing the statistical significance of drug-induced changes in other action potential characteristics at a single cycle length, a paired t-test was used to compare the ouabain-treated to the test drug-treated fiber.

Results

Transmembrane Potential Characteristics

The control transmembrane action potential characteristics for the 40 fibers studied [at cycle length (CL) = 500 msec] were: action potential amplitude, 127.5 ± 5.9 (mean ± SD) mV; maximum diastolic potential (MDP), −90.7 ± 5.5 mV; V_max, 604 ± 90 V/sec; duration (to full repolarization), 270 ± 12 msec. On superfusion with ouabain for 25–35 minutes, delayed afterdepolarizations occurred and on occasion initiated ectopic impulses. At this time, MDP at CL = 500 msec had decreased to −81.4 ± 7.3 mV, action potential amplitude to 113.4 ± 13.9 mV, and V_max to 479 ± 130 V/sec. Delayed afterdepolarizations occurred singly or as two to three afterdepolarizations in sequence, and their coupling to the preceding basic drive was related to the drive cycle length for the preparation. Ferrier et al. (1973) previously have discussed the relationship of the delayed afterdepolarization coupling interval to the basic cycle length. In this study, we were interested in the first delayed afterdepolarization that followed the action potential (Fig. 2). At drive CL ≥500 msec, these were the equivalent of the so-called “TD-1” (i.e., the first delayed afterdepolarization in a sequence) reported by Ferrier et al. (1973). At CL ≤300 msec, the first delayed afterdepolarization in a sequence usually was the equivalent of the “TD-2” of Ferrier et al. At CL = 400 msec, there was an equal proportion of both types of delayed afterdepolarizations. The numbers of preparations in which the delayed afterdepolarizations fired and initiated an action potential also are summarized in the legend of Figure 2. Note that at CL ≥400 only a small percentage of the delayed afterdepolarizations initiated action potentials. However, at a cycle length of 200 msec, 40% initiated action potentials. There appeared to be several reasons for the higher incidence of impulse initiation at the short cycle length. First, the delayed afterdepolarization amplitude and dv/dt at CL = 200 msec were significantly higher at CL = 200 msec than at longer cycle lengths (Fig. 2). It is likely that this higher delayed afterdepolarization amplitude and dv/dt at CL = 200 msec more readily would permit the fiber to attain threshold than at longer cycle lengths. In addition, on driving at a cycle length of 200 msec for 20 beats, resting membrane potential decreased from that seen at longer CL (Table 1B). This might bring the membrane potential closer to threshold and thereby increase the likelihood of the afterdepolarization attaining threshold potential and firing.

We did note one other interesting phenomenon that occurred concurrently with the delayed afterdepolarizations. In 15 preparations, phase 4 depolarizations fired and initiated an action potential.

Figure 2  Relationship between changes in basic drive cycle length (horizontal axis) to delayed afterdepolarization amplitude (amp), delayed afterdepolarization-coupling interval (DAD-C), delayed afterdepolarization mean rate of rise (dv/dt measured by dividing the voltage difference between MDP and DAD amplitude by the elapsed time) (vertical axis). Results of 40 experiments presented as mean ± SEM. At the basic cycle length of 200 msec, 16 of the 40 preparations developed afterdepolarization-induced action potentials; at a cycle length of 300 msec, 18 did so; at cycle lengths of 400, 500, and 600 msec, 3 did so; at cycle lengths of 800 and 1000 msec, 2 did so.
Polarization occurred prior to superfusion with ouabain. In most experiments, ouabain superfusion resulted in suppression of phase 4 depolarization as the delayed afterdepolarizations occurred. This has been described previously (Tsien and Carpenter, 1978). However, in four experiments, superfusion with ouabain increased the slope of phase 4 and also induced delayed afterdepolarizations in the same fiber. Moreover, in these instances, the slope of phase 4 was overdrive enhanced (as would be expected of delayed afterdepolarizations) rather than overdrive suppressed. These fibers had undergone a relatively greater loss of membrane potential as a result of superfusion with ouabain than most fibers in the study. Whereas, for the entire study, ouabain induced a decrease in MDP from $-90.7 \pm 3.7$ mV and expressed as mean ± sd. The AP characteristics in ouabain alone did not differ among the four groups.

### Pharmacological Studies

Of the drugs studied, all but AHR-2666 had a depressant effect on both action potential amplitude and $V_{\text{max}}$. The effects of the four drugs on these variables and on MDP at a drive cycle length of 500 msec are shown in Table 1A. Note that lidocaine, TTX, and verapamil all significantly decreased action potential amplitude and $V_{\text{max}}$, leaving MDP unchanged. AHR-2666, 45 mg/liter, not only did not depress any of these variables but, in some instances, by decreasing the amplitude of the delayed afterdepolarizations, thereby increased activation voltage for subsequent action potentials. This was accompanied by an increase in action potential amplitude (see Fig. 4) and $V_{\text{max}}$.

None of the drugs exerted a consistent or significant effect on the coupling of the delayed afterdepolarizations to the preceding action potential. All, however, significantly depressed both the amplitude and the dv/dt of the delayed afterdepolarizations. Because the effects on delayed afterdepolarization amplitude and dv/dt were approximately the same for each drug, we present here only the data on amplitude (Fig. 5).

All drugs significantly decreased delayed afterdepolarization amplitude at all cycle lengths studied ($P < 0.05$), and all eliminated the occurrence of delayed afterdepolarization-induced action potentials at all cycle lengths. However, as shown in Figure 5, the magnitude of drug effects at the various cycle lengths differed. Lidocaine, for example, had an equivalent depressant effect on delayed afterdepolarization amplitude at all basic cycle lengths. At CL = 1000 msec, lidocaine decreased afterdepolarization amplitude to 72% of the level that occurred with ouabain; at CL = 200 msec, amplitude was 64%. Although verapamil and AHR-2666 depressed delayed afterdepolarization amplitude at long cycle lengths (to 76% of ouabain), they depressed their amplitude to a significantly greater extent at short cycle lengths (37% of ouabain, $P <$...
The occurrence of enhanced automaticity and delayed afterdepolarizations induced by ouabain. This Purkinje fiber had been superfused with ouabain, \(2 \times 10^{-7} \text{ M}\), for 30 minutes. At a cycle length of 1000 msec, discontinuation of the drive stimulus was followed by an interval of diastolic depolarization and the onset of a stable automatic rhythm. This gradually increased in rate over several cycles. As the drive cycle length was decreased, the escape interval for the automatic focus decreased. This differs from the activity that would be expected with overdrive suppression of an \(i_{\text{K1}}\) dependent pacemaker. At cycle lengths of 300 and 260 msec, it can not be ascertained whether firing is due to a delayed afterdepolarization or to the automatic pacemaker. In all instances the final pacemaker rate attained is approximately the same whether at drive cycle lengths of 1000 or 260 msec. This is different from the behavior of delayed afterdepolarizations for which the final cycle length attained would be expected to be influenced by the basic drive cycle. Vertical calibration, 15 mV; horizontal, 2 sec; MDP, \(-73 \text{ mV at CL 1000-400 msec; -70 mV at 300-260 msec}\).

0.05). When ANOVA, nested for cycle length, was used to test for differences between the verapamil and AHR-2666 effects on delayed afterdepolarization amplitude over all cycle lengths studied, there were no differences between the two drugs \((P > 0.05)\). However, the action of lidocaine (depressing delayed afterdepolarization amplitude nearly equivalently at long and at short cycle lengths) differed significantly from that of verapamil and AHR-2666 \((P < 0.05)\). As for TTX, it had a greater effect on delayed afterdepolarizations at short (34% of ouabain) than at long (62% of ouabain) cycle lengths, and it differed both from AHR-verapamil \((P < 0.05)\) and from lidocaine \((P < 0.05)\). This analysis of the actions of the four drugs on delayed afterdepolarization amplitude over a wide range of cycle lengths suggests that effects are similar for AHR-verapamil and different for TTX and for lidocaine.

It is important to note that the effects of the test drugs on MDP did not differ from one another over the cycle lengths studied (see Table 1B). The effects of the drugs on action potential duration differed, however (Fig. 6). Neither verapamil nor AHR-2666 changed action potential duration, measured to full repolarization, from the values that were recorded during ouabain superfusion. However, both TTX and lidocaine significantly shortened action potential duration as compared to the values recorded for ouabain and those for AHR-2666 and verapamil \((P < 0.01)\).
Verapamil

DAD amp (mV)

BCL (msec)

FIGURE 5 Effects of verapamil (A), AHR-2666 (B), TTX (C), and lidocaine (D) on delayed afterdepolarization amplitude. The horizontal axes are the drive cycle lengths (msec); the vertical, delayed afterdepolarization amplitude (mV). The filled circles and bars are the mean ± SE for control amplitude; the unfilled circles and bars, amplitude following superfusion with the test drugs. None of the four control curves differed significantly from the others (P > 0.05).

Discussion

Several of our experiments indicated that delayed afterdepolarizations can occur either in the presence or the absence of digitalis-induced enhanced phase 4 depolarization. This observation is similar to one made by Hogan et al. (1973). Although they did not refer to the presence of both delayed afterdepolarizations and enhanced phase 4 in their paper, both events clearly occurred, as indicated by their Figures 1 and 2. A question to be considered here is what is the possible cause of the enhanced phase 4 depolarization. Aronson and Gelles (1977) have indicated that, perhaps as a result of poisoning of the Na-K pump and intracellular Na+ accumulation, digitalis reduces the amplitude of the iK2 inactivation curve. Both Aronson and Gelles (1977) and Tsien and Carpenter (1978) found that the iK2 mechanism for pacemaker initi-
larization in the same preparations indicates that either or both mechanisms could contribute to impulse initiation and arrhythmias.

The major observation in this study is related to the effects of AHR-2666, verapamil, lidocaine, and TTX on the amplitude of delayed afterdepolarizations and on their ability to initiate action potentials. All four drugs depressed afterdepolarization amplitude and up-stroke velocity and invariably prevented the afterdepolarizations from attaining threshold and initiating action potentials. None of the drugs significantly altered MDP. The only drug that had no effect on the action potential (AHR-2666) and a second drug that markedly decreased both action potential amplitude and upstroke velocity (verapamil) nonetheless had comparable effects on the afterdepolarizations. A third drug, TTX, that decreased action potential amplitude and upstroke velocity nonetheless depressed the delayed afterdepolarizations similarly, but not identically, to AHR-2666 and verapamil (i.e., it exerted a greater effect at short than at long cycle lengths). The action of TTX suggests strongly that the transient inward current responsible for delayed afterdepolarizations is TTX sensitive, an observation consistent with that of Vassalle and Scida (1979), but not with that of Kass et al. (1978). The latter suggested that TTX exerts a depressant effect on the transient inward current responsible for delayed afterdepolarizations only as a result of withdrawal of stimulation of the fibers (secondary to the effect of TTX on the action potential upstroke). Although we cannot entirely rule out an effect of TTX on the action potential upstroke resulting in depression of the afterdepolarizations, we found TTX to act promptly (within 5 minutes) to depress the afterdepolarizations, and it did not induce quiescence of the fibers. It might be argued that TTX, by depressing the action potential upstroke, is suppressing a trigger (the rapid inward Na⁺ current) for the delayed afterdepolarization, and it is this action which is responsible for the TTX-induced depression of the afterdepolarizations. However, verapamil, which depressed the action potential upstroke to an extent nearly equivalent to that of TTX, and AHR, which did not depress the action potential at all, had effects on the afterdepolarizations that were comparable to one another and different from that of TTX. Hence, it is likely that the effect of a drug such as TTX on the action potential upstroke is of minor importance in determining its action on delayed afterdepolarizations.

The effects of TTX on repolarization differed from those of AHR and verapamil (Fig. 6). The voltage-time course of the action potential was accelerated markedly, a result consistent with that reported by Coraboeuf et al. (1979). They attribute this action of TTX to the existence of a TTX-sensitive inward Na⁺ current, which is more sensitive to TTX than the rapid inward current, and which flows through a background conductance that either has no inactivation mechanism or one which is "abnormal" (Coraboeuf et al., 1979). The action of TTX on delayed afterdepolarizations might occur through such a channel, although this remains to be tested.

For lidocaine, the situation is different. The effect of lidocaine on the action potential amplitude and upstroke velocity of ouabain toxic fibers, although statistically significant, was small. Its effects on the delayed afterdepolarizations differed from those of the other drugs in that there were approximately equal decreases in delayed afterdepolarization amplitude at cycle lengths of 1000 and 200 msec and at all intervening cycle lengths. It is possible that lidocaine depresses the transient inward current responsible for digitalis-induced delayed afterdepolarizations. To our knowledge, such an action has not been reported yet. However, voltage clamp studies have shown that lidocaine's effects include both an increase in time independent outward current (i_Ki) and a decrease in background inward current (Weld and Bigger, 1976). Such actions could result in a decrease in delayed afterdepolarization amplitude over a wide range of cycle lengths. Moreover, the actions of both lidocaine and TTX on action potential duration (Fig. 6) would be consistent with an increase in outward repolarizing current (lidocaine) and/or a decrease in inward current (lidocaine, TTX)—not seen with AHR and verapamil.

A final factor to be considered in interpreting the results in Figure 6 is the following: as stated in the presentation of Figure 2, the majority of delayed afterdepolarizations that occurred at CL ≤300 msec are what Ferrier et al. (1973) termed TD-2. The differences in the four curves presented in Figure 5 are attributable, at least in part, to the effects of the drugs on delayed afterdepolarizations at very short cycle lengths. It may be that the ionic currents responsible for delayed afterdepolarizations at these very short cycle lengths are different from those that occur at longer cycle lengths. If this is the case, the currents are most highly sensitive to the calcium blockers, AHR and verapamil, least sensitive to an agent that does not modify calcium currents, lidocaine, and intermediate to sensitive to an agent to which some slow channel- and possibly Ca²⁺- blocking activity has been attributed, TTX (Bhattacharya and Vassalle, 1978).

The foregoing discussion of drug actions on delayed afterdepolarizations is highly speculative because of our incomplete knowledge of the mechanisms whereby drugs such as TTX, lidocaine, verapamil, and AHR-2666 affect ionic currents in mammalian cardiac fibers. What should be clear, however, is that the mechanisms responsible for the delayed afterdepolarizations and the attainment of threshold by delayed afterdepolarizations are complex and probably consist of a number of ionic
components, any one of which if appropriately modified can result in a decrease in the magnitude of the afterdepolarizations.

Additional information derived from this study concerns the relationship of effects of lidocaine on delayed afterdepolarizations in cellular electrophysiological studies to its actions on clinical arrhythmias that are induced by digitalis. It has been hypothesized that digitalis-induced arrhythmias characterized by repetitive ventricular responses are the result of delayed afterdepolarizations (Zipes et al., 1974; Rosen et al., 1975). To date, one of the major problems in reconciling the cellular mechanism with the clinical antiarrhythmic action has been the fact that most digitalis-induced ventricular arrhythmias respond well to lidocaine therapy, and lidocaine has not been thought to modify digitalis-induced afterdepolarizations. Our present observations show that a response to the effects of lidocaine during clinical digitalis toxicity or in experimental animals is totally consistent with the action of lidocaine on delayed afterdepolarizations, and hence, the response of an arrhythmia to this agent does not rule out afterdepolarizations as a possible cause.

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