this observation opens new avenues for research into the complex relationships which exist between protozoan parasites and their mammalian hosts.

Acknowledgment. This work was supported by grants from SECYT (Subsecretaria de Ciencia y Tecnologia) Argentina.

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0014-4754/88/010014-03$1.50 + 0.20/0

Tetrodotoxin slightly shortens action potential duration in ventricular but not in atrial heart muscle

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Summary. Tetrodotoxin (TTX), at concentrations significantly decreasing maximal upstroke velocity (dV/dt_{max}) of the action potential, exerted variable effects on action potential duration (APD) in different myocardial preparations. APD was virtually unchanged by tetrodotoxin in the guinea pig atrium, but slightly shortened in the guinea pig ventricle at maximally effective concentrations. In the human ventricle, both dV/dt_{max} and APD were reduced in the same concentration range of TTX. These results suggest that a TTX-sensitive sodium current significantly contributes to the repolarization phase of the action potential in ventricular but not in atrial heart muscle.
Key words. Atrial and ventricular myocardium; tetrodotoxin; window current; action potential configuration.

TTX has been reported to decrease APD in cardiac Purkinje fibers [1], at concentrations where an effect on dV/dt_{max} is not yet observed [2]. This finding was taken as evidence for the existence of a sodium window current possibly due to the significant overlap of the steady state activation and inactivation curves of the sodium system [3]. Experiments with lidocaine yielded similar results [4,5]. More direct evidence for a significant contribution of a sodium current to the repolarization phase in cardiac Purkinje fibers was presented by the demonstration of a persisting sodium current upon depolarization [6-8]. TTX shortens the action potential duration in Purkinje fibers to a much greater extent than in the working myocardium [2,9]. We show here the effects of TTX on intracellularly recorded action potentials from guinea pig heart (atrium and ventricle) and from human ventricular preparations obtained after cardiac surgery.

Methods. The preparations were obtained from freshly stunned guinea pigs and from human patients undergoing open heart surgery for mitral valve replacement (for details see Eckel et al. [10]). Right atrial and ventricular trabeculae and left human ventricular papillary muscle preparations were electrically driven at 1 Hz in Tyrode's solution (composition in mmol/l: NaCl, 136.9; KCl, 5.4; $MgCl_2$, 1.05; NaH_2PO_4, 0.42; $NaHCO_3$, 11.9; $CaCl_2$, 1.8; glucose, 5.6) bubbled with 95% O_2 and 5% CO_2 at 37 °C (pH 7.4). Action potentials were recorded intracellularly with conventional microelectrodes techniques and evaluated for duration at 20% and 90% of repolarization, APD_{20} and APD_{90}, respectively. The first time derivative (dV/dt) of the action potential was obtained by electronic differentiation and evaluated for dV/dt_{max}.

Results and discussion. In guinea pig atrial heart muscle, TTX decreased dV/dt_{max} in a concentration-dependent way, whereas APD remained virtually unchanged (figs 1a, 2a and 2b). In the guinea pig ventricle, dV/dt_{max} was decreased by TTX in the same concentration range and APD_{90} was slightly reduced at higher concentrations (figs 1b, 2c and 2d). In human ventricular heart muscle, both dV/dt_{max} and APD_{90} were reduced in the same concentration range (figs 1c and 3). In all preparations, the upstroke of the action potential was gradually decreased by cumulatively increasing concentrations of TTX and finally completely abolished, albeit at very high concentrations. In contrast, the effect of TTX on the repolarization phase was relatively weak (ventricular preparations) or virtually absent (atrial preparations). This shows that the contribution of a TTX-sensitive current to the repolarization phase of the action potential is relatively large in Purkinje fibers [1-3], relatively small in ventricular heart muscle [2,9] (this paper) and not significant in the atrium (this paper).

There are two possibilities to explain the quantitatively different results. First, a sodium window current may be differ-

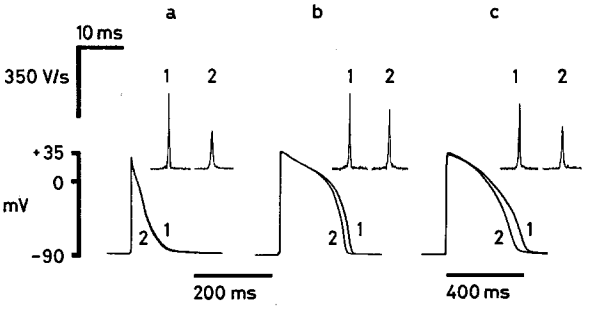

Figure 1. Effects of TTX 3×10^{-6} mol/l on dV/dt_{max} and APD in guinea pig atrium (a), guinea-pig ventricle (b) and human ventricle (c). Original records under control conditions (1) and 5 min after the addition of TTX (2) were superimposed (AP) or depicted side by side (dV/dt).

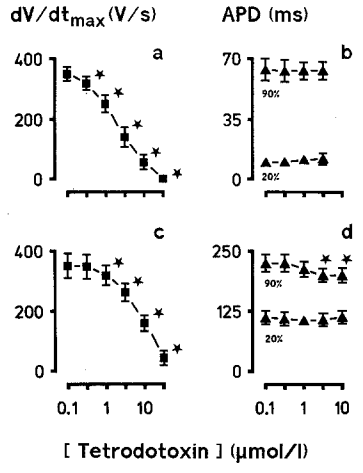

Figure 2. Effects of TTX on dV/dt_{max} (a,c) and APD (b,d) in guinea pig atrium (a,b; n = 6) and ventricle (c,d; n = 6). Concentration-response relationships obtained by cumulative addition (every 5 min) of TTX. Symbols depict means ± SEM. The asterisks denote statistically significant differences of test vs control values ($p < 0.05$ obtained by Student's t-test).

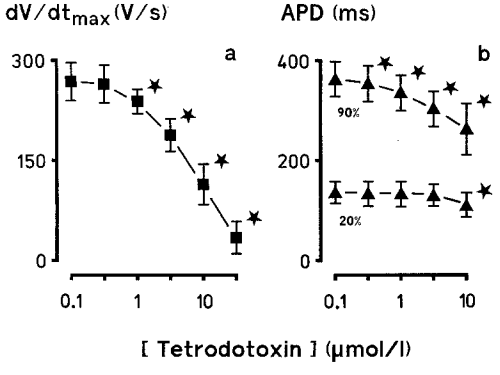

Figure 3. Effects of TTX on dV/dt_{max} (a) and APD (b) in human papillary muscle preparations. Concentration-response relationships obtained by cumulative addition (every 5 min) of TTX. Symbols depict means ± SEM. The asterisks denote statistically significant differences of test vs control values ($p < 0.05$ obtained by Student's t-test). n = 6.

ently developed in various regions of the heart. Second, the duration of the action potential in different regions of the heart may be influenced by differences in both calcium inward and potassium outward currents. As evident from ^{42}K washout experiments, the potassium permeability is higher in atrial[11] than in ventricular[12] heart muscle. Experiments in isolated singel cells have confirmed this concept[13]. In addition, the time constant of inactivation of the calcium inward current is shorter in atrial[14] than in ventricular preparations[15]. These additional factors may diminish the influence of a sodium window current of equal magnitude on the repolarization phase. It is unlikely that TTX affects other currents than the sodium inward current[16]. In this context, it is of interest to note that the effects of TTX persists in low-calcium solution (fig. 4a) and that the effects of TTX and the calcium antagonist (–)-desmethoxyverapamil[17] on the repolarization phase are additive (fig. 4b).

The observation that TTX has only minor or virtually no effects on the repolarization phase in heart muscle, is important in another context. Antiarrhythmic drugs are often classified with respect to their effects on action potential configuration, an effect on dV/dt_{max} being ascribed to the inhibition

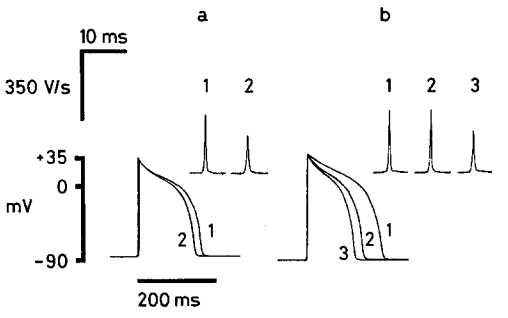

Figure 4. Effects of TTX 3×10^{-6} mol/l on dV/dt_{max} and APD of guinea pig ventricle in low (0.9 mmol/l) calcium (a) and in normal (1.8 mmol/l) calcium solution after the addition of (–)-desmethoxyverapamil 10^{-6} mol/l (b). Original records both under control and test conditions were superimposed (AP) or depicted side by side (dV/dt). In (a), records were obtained under control conditions (1) and 5 min after the addition of TTX (2). In (b), records were obtained under control conditions (1), 30 min after the addition of (–)-desmethoxyverapamil (2), and 5 min after further addition of TTX (3). Note that, in contrast to TTX, the calcium antagonist markedly shortened APD without an influence on dV/dt_{max}. Similar results were obtained in two other preparations from guinea pigs and in one human ventricular heart muscle preparation.

of sodium inward current (local anesthetic effects similar to the effects of TTX) and an effect on the repolarization phase being ascribed to an interference with potassium/calcium currents[18]. This approach to drug classification remains problematic but may yield clearer results in preparations from the working myocardium than in Purkinje fibers.

* Supported by the Deutsche Forschungsgemeinschaft (Na 105/5–5) and by the Fonds der Chemischen Industrie. Author to whom reprint requests should be addressed. We thank Mrs. Johanna Rupp for expert technical help. We also thank one referee for suggesting the experiments depicted in figure 4.

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