Lidocaine’s Negative Inotropic and Antiarrhythmic Actions

Dependence on Shortening of Action Potential Duration and Reduction of Intracellular Sodium Activity

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SUMMARY. The mechanisms by which lidocaine brings about negative inotropic effects and antiarrhythmic actions in the heart have been examined. Using sheep cardiac Purkinje fibers, we studied the effects of "therapeutic" concentrations of lidocaine (20 μM lidocaine = 5.4 μg/ml) on electrical activity, intracellular sodium activity, and tension. For the preparation with a normal, physiological level of intracellular sodium activity (5–9 mM), the application of lidocaine leads to the following actions: (1) action potential duration is decreased, (2) intracellular sodium activity falls, and (3) twitch tension is reduced. If intracellular sodium activity is first elevated (e.g., by sodium pump inhibition) so that arrhythmogenic transient depolarizations (and the underlying transient inward current are seen) then lidocaine has the following actions: (1) The action potential duration is reduced. (2) There is a reduction of the magnitude of the arrhythmogenic transient depolarization (or the underlying membrane current transient inward current). (3) The magnitude of the aftercontraction that accompanies the transient depolarization (or transient inward current) is reduced. (4) If, after sodium pump inhibition, intracellular sodium activity is still rising—then, the application of lidocaine leads to a reduction of the rate of rise of intracellular sodium. From these results, parallel voltage-clamp experiments, and recent work by others, we conclude that lidocaine leads to the reduction of the arrhythmogenic transient depolarization and a reduction of twitch tension by decreasing the inward sodium current. These actions are mediated by a reduction in action potential duration and a reduction of intracellular sodium activity and of intracellular calcium activity (by the sodium-calcium exchange mechanism). (Circ Res 57: 578-590, 1985)

ANTIARRHYTHMIC agents have been classified according to their putative mechanism of action for a number of years (cf. Vaughan-Williams, 1974; Hauswirth and Singh, 1979; Rosen and Wit, 1983). More recently, however, multiple cellular actions of antiarrhythmic agents have been demonstrated. Lidocaine, a sodium channel blocker, has been reported to alter potassium currents (Bigger and Mandel, 1970; Weld and Bigger, 1976; Arnsdorf and Bigger, 1972) and, more recently, to reduce the mixed cation pacemaker current, I (Carmeliet and Saikawa, 1982). Although not used clinically as an antiarrhythmic agent, tetracaine, another sodium channel blocker, also has been shown to affect the release of calcium from the sarcoplasmic reticulum (Almers and Best, 1976). Quinidine, a third sodium channel blocker, has been reported to block the Na+-Ca++ exchange mechanism (e.g., Mentrard et al., 1984), as well as to inhibit potassium currents (cf. Colatsky, 1982). The present study is designed to examine the antiarrhythmic actions of lidocaine at therapeutic concentrations (20 μM or 5.4 μg/ml). Work to date examining the action of lidocaine has shown that this agent has a number of important and relevant features.

1. The maximal rate of rise of the action potential, (dV/dt)max, is reduced by lidocaine (Chen et al., 1975). This has been taken as evidence that the peak inward sodium current is reduced by lidocaine (but, see, e.g., Cohen et al., 1984).

2. Under voltage clamp conditions, the peak I Na is reduced by lidocaine (Lee et al., 1981; Bean et al., 1983; Sanchez-Chapula et al., 1983).

3. Lidocaine shortens the cardiac action potential (Davis and Temte, 1969; Bigger and Mandel, 1970; Colatsky, 1982).

4. "Use-dependent" development of the lidocaine blockade of sodium channels has been reported, a finding consistent with the requirements of a modulated-receptor hypothesis (Hondegem and Katzung, 1977; Hille, 1977; Bean et al., 1983).

5. The steady state I Na window current (Attwell et al., 1979) is reduced by the application of lidocaine (Colatsky, 1982). Lidocaine can therefore block a fraction of the activated sodium channels that do not inactivate during the plateau of the action potential, and thereby reduce action potential duration (Colatsky, 1982; Bean et al., 1983).

Despite these well known actions of lidocaine, it is still uncertain whether the degree of blockade of
the sodium channel by lidocaine is sufficient at therapeutic concentrations to explain its powerful anti-arrhythmic action, as well as its negative inotropic actions. In this paper, we report on experiments that examine the ability of lidocaine to alter mechanical and electrical activity in sheep cardiac Purkinje fibers. The work involves measuring intracellular sodium activity (aSH) and tension while simultaneously stimulating action potentials or controlling membrane potential with a voltage clamp technique. We find that the negative inotropic action and the antiarrhythmic action of lidocaine can be attributed to its ability to block sodium channels and thereby reduce sodium current, I Na (cf. Colatsky, 1982; Eisner et al., 1983a; Bean et al., 1983). These actions are mediated by (1) reduction in action potential duration (producing a rapid effect) and (2) a decrease in aSH, which produces a secondary slower effect.

A preliminary communication of this report was made to the American Physiological Society (Sheu and Lederer, 1983).

Methods

General Methods

Purkinje fibers were taken from the hearts of freshly killed sheep obtained from a local slaughterhouse. Free-running fibers from either ventricle were placed in oxygenated, modified Tyrode's solution at room temperature. Fibers were shortened and placed in the superfusion bath described by Eisner and Lederer (1979b). For all voltage clamp experiments, the fibers were shortened to less than 2 mm long. The contractile conductive core of the Purkinje fibers was less than 0.3 mm in diameter. In other experiments, action potentials were elicited by field stimulation. Tension was measured in all experiments using a piezoresistive element described by Eisner and Lederer (1979b).

Intracellular Sodium Activity

Intracellular sodium activity was measured with a liquid ion exchange (ETH 227) in a solvent cocktail kindly given to us by Professor Simon and Dr. Ammann of the Swiss Federal Institute of Technology (ETH), Zurich, Switzerland. This ionophore cocktail is available commercially from Fluka Chemical Corporation (no. 71176). The methods used to construct the intracellular sodium-sensitive microelectrodes and their calibration have been described elsewhere (Sheu and Fozzard, 1982; Eisner et al., 1983a). Lidocaine hydrochloride has a small effect on sodium conductive properties.

The "intracellular sodium signal" is obtained by subtracting the membrane potential (obtained with a standard 3 m KCl microelectrode) from the voltage signal produced by the sodium-selective microelectrode. This unprocessed intracellular sodium signal was recorded on magnetic tape to permit the complete analysis after an experiment. The differences in the resistances of the two electrodes combined with the capacitance of the electrodes leads to significant artifacts in the intracellular sodium signal whenever membrane potential is changing rapidly and by a large amount. In the figures shown, we have removed the artifactual variations of measured aSH by filtering the intracellular sodium signal with an eight-pole low-pass Bessel filter (Frequency Devices) with a cut-off frequency of between 1 and 0.2 Hz. Since such filtering could, in principle, lead to inaccuracies in the measured intracellular sodium, we have done the following to guard against such errors. (1) We have demonstrated that the unfiltered intracellular sodium signal associated with one action potential had reached a steady state prior to the next stimulated action potential (i.e., the integral of the artifactual signal was zero). (2) We have shown that the time course and the measured values of intracellular sodium (just prior to the stimulated action potential) follow the same time course and values as that of the filtered signal. (3) We confirmed that abrupt changes in stimulation rate from 0 to the highest rates seen in these experiments did not change aSH. As suggested here and demonstrated elsewhere (Cohen et al., 1982; Lederer and Sheu, 1983), sustained changes in stimulation rate produce genuine increases in aSH.

Solutions

The standard superfusion solution contained (in mm): NaCl, 145; KCl, 4; CaCl2, 2; MgCl2, 1; Tris-HCl, 10; glucose, 10; pH 7.4. Any modification of the standard solution is noted in the text. Lidocaine hydrochloride (Pfaltz and Bauer) was added as a solid directly to a stock of the superfusion solution. Strophanthinidin (Sigma) was made up as a 2.0 X 10⁻² M solution in ethanol and stored at -20°C until required.

Terminology

The arrhythmogenic transient inward current has been referred to by a number of different names including I r, I w, I a, and I h. We have chosen to use I h in place of the other terms. In addition, we shall refer to the initial oscillation in membrane potential as a transient depolarization or TD. This term is equivalent to those used by others, including afterdepolarization, triggered afterpotential, and delayed afterdepolarization (DAD). The oscillation in tension that accompanies the I h or the TD will be called the aftercontraction or AC, although other names have been used to describe this phenomenon as well.

Results

Working Hypothesis

In this paper, we plan to test the hypothesis that lidocaine's inotropic and electrical actions are a consequence of its ability to block sodium channels. We shall therefore examine how lidocaine reduces twitch tension, and how it abolishes triggered arrhythmias. We will focus on the changes in electrical activity and the changes in intracellular sodium ion activity brought about by the application of lidocaine because of the respective rapid and slower time courses of the effects.
Negative Inotropic Action of Lidocaine

Lidocaine Reduces $a_{\text{Na}}$ and Action Potential Duration

Figure 1 illustrates the effects of adding 20 $\mu$M lidocaine to the solution bathing an isolated Purkinje fiber (seen in five other experimental trials). Figure 1A shows superimposed action potentials (above) and twitches (below) to compare the effects of lidocaine (record b) to pre- and post-exposure action potentials, (records a and c, respectively) obtained in the absence of lidocaine. The time course of the action of lidocaine to reduce $a_{\text{Na}}$ and tension is shown in panel B. Action potential duration (measured at 75% repolarization) is plotted as a function of time in panel C. The reduced action potential duration produced by lidocaine has been observed by many workers (e.g., Davis and Temte, 1969; Bigger and Mandel, 1970) and is expected, since Colatsky (1982) showed that a significant and measurable steady state $I_{\text{Na}}$ current exists over the range of membrane potentials found during the plateau of the action potential. This tetrodotoxin (TTX)-sensitive current is thought to constitute a $I_{\text{Na}}$ window current (Attwell et al., 1979) that arises from the overlap of the steady state activation and inactivation curves. The decrease in intracellular sodium ($a_{\text{Na}}$) that is seen in Figure 1 is therefore expected because lidocaine, like TTX, can reduce $I_{\text{Na}}$ over the range of membrane potential that is produced during the plateau of the action potential.

Role of Action Potential Duration

An important unanswered question is whether the reduction of tension that is produced by lidocaine is appropriate for the measured change in $a_{\text{Na}}$ (cf. Eisner et al., 1984). Figure 2 addresses this issue and shows the result of one of the three similar experimental trials. Figure 2A shows experimental results from a preparation different than that used for the experiment illustrated in Figure 1. The time courses of the fall in action potential duration (APD), twitch tension, and $a_{\text{Na}}$ are illustrated. The most
striking difference between this experiment and the one illustrated in Figure 1 is that, in Figure 2, the APD is reduced much more rapidly by the application of lidocaine. To estimate the relative influence of the action potential duration changes vs. the effects of $a_{Na}$, it is helpful to examine Figure 2A closely. In this experiment, the action potential duration decreases rapidly, before there is a measurable change in $a_{Na}$. The fact that twitch tension has decreased by 41% independent of any change in $a_{Na}$ suggests that nearly half of the change in tension may arise from the change in action potential duration (see Discussion).

**Role of $a_{Na}$**

The experiment in Figure 2A shows that, once changes in action potential duration are virtually complete, further changes in twitch tension occur. These secondary changes in tension are accompanied by a fall in $a_{Na}$. The experiment shown in Figure 2A is noteworthy because it shows a clear separation of the time course of changes in action potential duration from that of $a_{Na}$ changes. After the initial 41% fall in tension associated with nearly all of the reduction in action potential duration that occurs, $a_{Na}$ starts to fall. Figure 2, B and C, shows the relationship between twitch tension and $a_{Na}$ on logarithmic axes taken from the experiments shown in Figures 2A and 1, respectively. Under the conditions of this experiment, the straight line that has been fit to the data of Figure 2B suggests that the dependence of tension on sodium may be a power function, just as it is when the duration of a depolarizing pulse is fixed by voltage clamp control (Eisen et al., 1983b, 1984):

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\text{Twitch tension} = b(a_{Na})^N
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where $N$ is the slope of the line in Figure 2B.

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**Figure 2.** The steep relationship between intracellular sodium activity and tension. Panel A: time course of the effects of 20 $\mu$M lidocaine on action potential duration, twitch tension, and intracellular sodium. Note that the action potential duration is reduced to 91% of its steady state reduction, and twitch tension is reduced to 41% of its steady state value before any reduction of $a_{Na}$ is observed. There is no such clear separation of effects of action potential duration and $a_{Na}$ in the experiment shown in Figure 1. Panel B: the relationship between tension and $a_{Na}$ is plotted on logarithmic coordinates. The control level is indicated with a cross. On application of lidocaine (20 $\mu$M) at the first measured fall of $a_{Na}$, equally spaced data points were obtained and are shown by filled circles. The straight line is the least-squares best-fit line to the data where the slope = 4.31 and the coefficient of determination = 0.82. The open circles show data during the recovery from lidocaine exposure, also obtained at equal time intervals. The dashed line is the least-squares best-fit line to the data where the slope = 5.8 and the coefficient of determination = 0.91. Panel C: plot of data from the experiment shown in Figure 1. Cross-control; closed circle-data on exposure to lidocaine (20 $\mu$M), at equally spaced intervals. The straight line is the least-squares best-fit line to the data where the slope = 4.5 and the coefficient of determination = 0.99.
a depolarizing pulse is fixed, the average N equals 3.2, is independent of a Na, of membrane potential (Eisner et al., 1983b, 1984), and of intracellular pH (M.B. Cannell, W.J. Lederer, and R.D. Vaughan-Jones, unpublished). The slope of the solid line in Figure 2B is 4.3 (coefficient of determination of 0.82), a value consistent with that reported in voltage clamp studies in the sheep Purkinje fiber preparation (Eisner et al., 1983b, 1984). Consequently, even the small changes of a Na seen during the application of lidocaine would appear adequate to explain the fall in force that is seen clinically when this agent or other local anesthetics are used. However, as described above, there is an additional negative inotropic effect of reducing the action potential duration (see Gibbons and Fozzard, 1975, and Discussion). In these experiments, we have attempted to differentiate between these two actions of lidocaine by taking advantage of the variation in the timing of the two effects. The dependence of tension on a Na shown during the recovery from lidocaine is different from that during the exposure (see Fig. 2, B and C). The larger values of N observed may reflect the varying influence of action potential duration and a Na on tension. The different magnitudes by which action potential duration and a Na change with the application and removal of lidocaine are shown in Figures 1B and 2A (see Discussion).

Antiarrhythmic Action of Lidocaine

Figure 3 shows an experiment in which the application of lidocaine (20 µM) abolishes a triggered cardiac arrhythmia (cf. Eisner and Lederer, 1979a). Results qualitatively similar to this have been observed in three other experiments. The triggered action potentials developed in an isolated Purkinje fiber after it was exposed to a toxic concentration of strophanthidin (0.5 µM). These triggered extrasystoles are abolished by the application of lidocaine.

Dependence of Triggered Extrasystoles on a Na

Panel I shows records obtained after the preparation was exposed to 0.5 µM strophanthidin for about 20 minutes. The blockade of the sodium pump (produced by 0.5 µM strophanthidin) leads to an increase of a Na. In panel I, at the time indicated by the solid bar above record B, the preparation developed erratic ectopy which led to sustained triggered extrasystoles. The action potentials are shown in panel II in greater detail. The extrasystoles developed as a Na was rising and resulted from transient depolarizations that reached threshold (Ferrier et al., 1973; Ferrier, 1977). The development of such transient depolarizations ("TD" see discussion of other equivalent terms in Methods) has been associated with the development of ectopy in intact experimental animals using cross-perfusion experiments (Rosen et al., 1973a, b). Voltage clamp experiments have shown that a calcium-activated membrane current called I Na is responsible for the arrhythmogenic transient depolarizations (Lederer and Tsien, 1976; Kass et al., 1978a, 1978b; cf. Colquhoun et al., 1981), although there is some controversy about cellular process that produces this current (cf. Noble, 1984; Arlock and Katzung, 1985).

Positive Feedback Effect of Extrasystoles

At the time that triggered extrasystoles develop, there is an increase in the rate of rise of intracellular sodium. This presumably reflects the action of increased number of action potentials per second (a doubling, in this case) and is consistent with the rate dependence of a Na that has been reported previously (Cohen et al., 1982; Lederer and Sheu, 1983). To the extent that a rise in intracellular sodium is associated with an increase in the magnitude of the arrhythmogenic transient inward current, I Na, re-
sponsible for the triggered extrasystoles (Eisner et al., 1983a; cf. Lederer and Tsien, 1976), this increased rate of rise of $\alpha_{Na}$ represents a positive feedback. Thus, once triggered extrasystoles develop, they will not only sustain themselves, but will also accelerate their rate of production if such positive feedback occurs. Note in Figure 3 that the time between the stimulated action potential and the triggered extrasystole gets continually shorter and shorter as is predicted from such a positive feedback mechanism.

Immediate Antiarrhythmic Action of Lidocaine

The portion of the experimental record above the bar labeled "C" in panel I of Figure 3 is shown in detail in panel II. Within 8 seconds of the addition of lidocaine (20 $\mu$M), the extrasystoles are abolished. Initially, there are progressively longer periods between the stimulated action potential and the triggered extrasystole until, at the time labeled "C" in panel II, the "transient depolarization" does not reach threshold and no extrasystole occurs. It is clear, however, that during the nearly 2 minutes after the application of lidocaine (shown in Fig. 3, panel I), $\alpha_{Na}$ does not change. Thus, there is no reduction of $\alpha_{Na}$ associated with the abolition of the ectopy.

Effect of Altered Action Potential Duration on Arrhythmias

There is an immediate reduction in the duration of the action potential when lidocaine is applied. This immediate reduction of action potential duration can be seen in Figure 4, trace b. Even after the abolition of extrasystoles (trace c), the action potential duration continues to decrease (trace d). Presumably, this reflects the time course of development of the steady state effects of lidocaine. The effects of the reduction of the action potential duration on the transient depolarization seen here, and reported by Henning and Wit (1984), are consistent with the earlier voltage clamp investigations of the effects of depolarization duration on $I_{Na}$ (Lederer and Tsien, 1976; Kass et al., 1978a).

Effects of Depolarization Period on $\alpha_{Na}$ and $I_{Na}$

In the absence of a steady state, voltage-dependent "window" conductance for sodium, one would expect that sodium entry would decrease as the electrochemical driving force for sodium ($E_{Na} - V_m$) decreased. Under these conditions, depolarizing the membrane potential from the maximum diastolic potential to a plateau potential (about $-30$ to $+10$ mV) should lead to decreased sodium entry. How-

![Figure 4](http://circres.ahajournals.org/)

The action of lidocaine to abolish spontaneous activity by shortening action potential duration. Specimen records are obtained (and superimposed) from the experiment illustrated in Figure 3 at the times indicated by the small letters. Trace a: sustained bigeminy. Note that the left-hand action potentials and the right-hand action potentials have been triggered by external shocks applied at 1.0 Hz. The spontaneous action potential in the middle associated with the bigeminy (prior to the application of lidocaine) is the one occurring first, and is associated with the most marked pacemaker depolarization. Furthermore, it is associated with the longest action potential duration of both the stimulated action potential and of the extrasystolic action potential. Trace b: 6 seconds after the application of lidocaine (20 $\mu$M), there is a clear shortening of the stimulated action potential associated with a reduced pacemaker depolarization and a delay of the extrasystole. Record c: 8 seconds after the application of lidocaine (20 $\mu$M), the stimulated action potential is shorter still, the pacemaker depolarization is reduced even further, and, whereas the transient depolarization is clearly present, it does not lead to an extrasystole. Record d: about 1 minute after the addition of lidocaine (20 $\mu$M), the shortest of the four action potentials is seen, pacemaker depolarization is also the least of the four records shown, and the transient depolarization magnitude is very small.
ever, this tendency of depolarization to decrease sodium entry will be opposed by the established presence of a "window" of increased steady state sodium conductance ($g_{N_{\infty}}$) at plateau potentials (cf. Attwell et al., 1979; Colatsky, 1982). Thus, the experiments in Figures 1–4 show examples where the effects of decreased $g_{N_{\infty}}$ brought about by the application of lidocaine and the decreased mean ($E_{N_{\infty}} - V_m$) due to the shorter action potential combine to reduce sodium entry and $a_{N_{\infty}}$. Earlier voltage clamp experiments (e.g., Eisner et al., 1981, 1982, 1983b; January and Fozzard, 1984) have shown that with depolarization there can be a decrease in $a_{N_{\infty}}$. This has raised the question—when there are changes in action potential duration alone, in the absence of pharmacologically induced decreased $g_{N_{\infty}}$ (e.g., application of lidocaine)—does $a_{N_{\infty}}$ fall. Furthermore, this raises the question of how changes in action potential duration per se are related to $I_{\text{T}}$ and $a_{N_{\infty}}$. Figure 5A shows a voltage clamp experiment that was carried out in the absence of lidocaine and was designed to test these questions. These results are similar to those seen in five other experimental trials. It shows how the voltage clamp equivalent of shortening the action potential duration affects $a_{N_{\infty}}$ and $I_{\text{T}}$. With the sodium pump partially blocked by strophanthidin (0.1 µM), sheep cardiac Purkinje fibers were depolarized under voltage clamp control for 3 seconds to $-26$ mV, and then the membrane potential was returned to $-51$ mV for 4 seconds. After the period of depolarization, there is a clear oscillatory transient inward current, $I_{\text{n}}$. An aftercontraction accompanies the $I_{\text{T}}$, reflecting the phasic rise of intracellular calcium that follows the depolarization, and which is responsible for both the calcium-activated current $I_{\text{T}}$ and the aftercontraction seen in Figure 4 (Lederer and Tsien, 1976; Kass et al., 1978a, 1978b; Wier and Hess, 1984; Eisner and Valdeolmillos, 1985). As indicated in Figure 5B, when the period of depolarization was reduced to 1 second, there was an immediate reduction in $I_{\text{T}}$ magnitude but no similar effect on $a_{N_{\infty}}$. However, there was a small secondary increase in $a_{N_{\infty}}$ that did develop along with a parallel increase in $I_{\text{T}}$ and aftercontraction, and a small increase in twitch tension. This secondary increase in $a_{N_{\infty}}$ indicates that the increase in electrochemical gradient for sodium entry was more important under these conditions than the decrease in $g_{N_{\infty}}$. Under these conditions, it is the secondary increase in $a_{N_{\infty}}$ (and of an $a_{L_{\infty}}$ via the Na$^+$-Ca$^{2+}$ exchange) that is important in producing the secondary increase in $I_{\text{T}}$ (cf. Eisner et al., 1983a). We will not analyze twitch tension in these experiments (when $a_{N_{\infty}}$ is significantly elevated by sodium pump inhibition) because the 'calcium overload' and the intracellular calcium oscillations that develop (cf. Kass and Tsien, 1982; Matsuda et al., 1982; Orchard et al., 1983; Wier et al., 1983) lead to alterations in the normal links between calcium release and twitch tension development (cf. Kort and Lakatta, 1984; Cannell et al., 1985). Under these conditions, twitch tension is a relatively complex function of the ionic environment, as evidenced by reports of increases in tension with reduced extra-
cellular calcium (Vassalle and Lin, 1979; Bhattacharyya and Vassalle, 1981), or the fall in twitch tension with rising $a_{N_{\infty}}$ (Eisner et al., 1983c, 1984). Nevertheless, it is this same calcium-overload condition
that gives rise to $I_N$ and the associated aftercontraction. Figure 5B shows the time course of the change of $I_N$ magnitude, aftercontraction size, and $a_{IN}$ level following the change in voltage clamp-depolarizing pulse duration. Whereas $a_{IN}$ is unchanged, there is a nearly immediate reduction of $I_N$. This rapid attenuation of $I_N$ is similar in speed to the reduction of ectopy and transient depolarization magnitude shown in Figure 4 (occurring over seconds). The fall in $I_N$ magnitude presumably reflects the reduction in the calcium released by the sarcoplasmic reticulum (cf. Lederer and Tsien, 1976; Kass et al., 1978a) due solely to a shorter period of depolarization, since no lidocaine was applied. Exactly how action potential duration can affect $I_N$ is not known, but, as suggested above, it may depend on the potential-dependent calcium flux into the cytosol and the action of the increased $Ca_{in}$ load on the sarcoplasmic reticulum. The experiments presented here do suggest that, in the case of lidocaine, there is no need to postulate an additional drug effect, since the shortening of the action potential duration (or voltage clamp pulse duration) is sufficient to explain the immediate action. Thus, it would appear as if lidocaine’s immediate action to reduce $I_N$ and transient depolarizations, can be fully explained by the action of this drug to reduce action potential duration. Following this immediate action, Figure 5 shows that there is a secondary increase in $I_N$ magnitude and aftercontraction magnitude which are paralleled by an increase in $a_{IN}$. This secondary increase in $a_{IN}$ was not seen in the other experiments shown in Figures 1-4. The time-dependent increase in $a_{IN}$ (and $I_N$) may reflect the voltage-dependent changes in $a_{IN}$ previously reported (Eisner et al., 1981, 1982, 1983b, 1983c; January and Fozzard, 1984), since the mean driving force for the entry of $Na^+$ ($E_{Na} - V_m$) has increased.

**Discussion**

The working hypothesis on which we have based our experiments is that lidocaine’s negative inotropic action and its antiarrhythmic action result from lidocaine’s blockade of $I_N$. Schematically, this is illustrated in Figure 6.

Figure 6 shows how we believe lidocaine acts to reduce twitch tension and to antagonize cardiac arrhythmias, and is consistent with our findings and with the reports of others. Lidocaine reduces the rapidly inactivating component of $I_N$ (cf. Bean et al., 1983) and the steady state $I_N$, "window" current (Colatsky, 1982) which is observed during the plateau of the action potential. The reduction of $I_N$ decreases sodium influx directly, and is responsible for the shortening of the action potential duration that we and others have observed. Although the $I_N$ seen during the plateau is small, compared to $I_N$ at its peak, the duration of the plateau is very much longer. Thus, significant sodium influx can occur during the plateau of the action potential. Eisner et al. (1983a) have concluded that, at least over plateau potentials, lidocaine’s principal action is to block $I_N$ and does not markedly alter other membrane currents (but see also Colatsky, 1982). This finding of Eisner et al. (1983a) is based on a comparison of the magnitude of the rapid change in current produced by the addition of lidocaine to the change in $a_{IN}$ seen at the same time. Sodium influx is therefore reduced, because lidocaine blocks some sodium channels and also because the shorter action poten-

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**Figure 6. Schematic diagram showing how lidocaine may antagonize cardiac arrhythmias.** Lidocaine acts principally to reduce $I_N$, and this reduction has three principal actions: 1) The reduced $I_N$ will move the threshold for excitation to a more positive potential. The more positive threshold will tend to antagonize some re-entrant arrhythmias and will decrease the probability that $I_N$ will produce a transient depolarization that triggers an extrasystole; 2) The reduced $I_N$ will shorten the action potential duration. Because sodium and calcium ions can enter through an $I_N$, "window" and an $I_T$, "window" that exist over plateau potentials, shorter action potentials will lead to diminished sodium-influx and calcium-influx (by this mechanism). Note however, that at a fixed heart rate, a shorter action potential duration will lead to an additional effect that will tend to increase $a_{Na}$ and $a_{Ca}$. Under these conditions the average electrochemical gradient more greatly favors the entry of sodium and calcium. The relative importance of these opposing actions of a reduced APD is addressed in the text. While the "immediate" actions of lidocaine and reduced APD are presumably mediated by a fall in calcium entry leading to a fall in the magnitude of the calcium transients, other possibilities are presented in the Discussion; 3) The reduction of $I_N$ leads to a direct reduction of sodium-influx. By actions 2 and 3, lidocaine frequently leads to a fall in $a_{IN}$ which in turn leads to a reduction of the calcium transient responsible for the twitch and a reduction of the calcium transient responsible for $I_N$. 

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tial decreases the time available for sodium influx through the sodium channels that are unblocked and have not inactivated. The above mechanisms underlie lidocaine’s reduction of intracellular sodium (see our Figures 1 and 2, and Deitmer and Ellis, 1980a; Eisner et al., 1983a) and, via the Na$^{+}$-Ca$^{++}$ exchange, the reduction of intracellular calcium. This fall of mean cytosolic calcium by lidocaine has not yet been measured directly, but is expected from previous examination of $a_{na}$ and $a_{ra}$ (Sheu and Fozzard, 1982). It should lead to less calcium uptake and release by the sarcoplasmic reticulum. Thus, the reduction of $a_{na}$ is responsible for part of the negative inotropic and part of the antiarhythmic actions of lidocaine that we have reported. Furthermore, the shorter action potential that is produced by lidocaine should decrease calcium influx through non-inactivating calcium channels [cf. $d_{ca}$ and $f_{ca}$ curves of Reuter (1974) and Kass and Sanguinetti (1984)] and the voltage-dependent Na$^{+}$-Ca$^{++}$ exchange. The decrease in calcium influx will lead to a reduction of cytosolic free calcium, and thereby have a rapid effect on the amount of calcium being taken up and released by the sarcoplasmic reticulum. It is consequently the decrease in intracellular calcium that more directly leads to the fall of twitch tension (but see below) and the reduction in “calcium overload” and the reduction of the arrhythmogenic current $I_{Na}$ (cf. model of Kass et al., 1978a). Finally, the reduction in $I_{Na}$ is responsible for shifting the threshold for triggering an action potential to more positive potentials. With a more positive excitation threshold, an $I_{Na}$ of a fixed magnitude that may follow an action potential is less likely to produce a transient depolarization that triggers an arrhythmia.

**Lidocaine’s Action on Peak $I_{Na}$ vs. Its Action on Plateau $I_{Na}$**

Lidocaine or other agents which block sodium channels will affect sodium influx during the upstroke of the action potential, as well as during the plateau of the action potential. In view of the previous discussion, it seems worthwhile to estimate the relative contributions to the total sodium influx from the inactivating portion of $I_{Na}$ as compared to the steady state $I_{Na}$ “window” current. By extrapolating from experiments carried out at low sodium and in the cold, Colatsky (1980) has estimated that a peak inward sodium current of about 500 $\mu$A/cm$^2$ exists in rabbit cardiac Purkinje fibers in 150 mM NaCl at 37°C. At a potential of $-20$ mV, the time constant of inactivation ($r_h$) of $I_{Na}$ was estimated to be between 0.4 and 0.7 msec. Because of the marked decrease in these values with the more positive potentials (the overshoot of the action potential may be as positive as $+40$ mV), the actual $r_h$ may be much smaller (see DiFrancesco and Noble, 1985). Assuming that $r_h$ of $I_{Na}$ during the action potential is about 0.14 msec, the flux associated with peak $I_{Na}$ would be about 0.7 pmol/cm$^2$ per action potential. That compares to a flux of about 1.0 pmol/cm$^2$ per action potential for a steady state sodium influx during a 500-msec plateau (mean current level at about 0.2 $\mu$A/cm$^2$) (cf. Colatsky, 1982). Using the above assumptions, experimental observations and estimates, the flux of sodium during the plateau of the action potential is comparable to that seen during the upstroke of the action potential. This example suggests that if the action potential duration decreased by 33%, the peak sodium influx will be unaffected but the “window” flux will decrease by 33%. This would lead to a decrease in the total influx per action potential of about 20%.

**Can Lidocaine’s Antiarrhythmic Action Be Explained by Its Action on Something Other Than $I_{Na}$?**

Rosen and Danilo (1980) have presented some evidence suggesting that lidocaine acts to block $I_{Na}$ or the transient depolarization by directly affecting membrane currents other than $I_{Na}$. Eisner et al. (1983a) argue against this possibility, making the following points: (1) the rapid reduction of inward current produced by the application of lidocaine is quantitatively appropriate to explain the rate of fall of $a_{na}$ only if lidocaine is blocking an inward sodium current. (2) The time course of change of $I_{Na}$ follows the time course of the change of intracellular sodium. (3) Two agents known to alter intracellular sodium produce a similar relationship between intracellular sodium and $I_{Na}$, as does lidocaine (TTX—the sodium channel blocker, and rubidium—when it reactivates a partially blocked sodium pump). Our experiments also support the conclusions of Eisner et al. (1983a). There is, however, some variability in the experimental results that we observe. The experiment shown in Figures 3 and 4 represents the first of two classes of results that we have obtained when we add lidocaine to a preparation exhibiting transient depolarizations or extrasystoles. In the second class of results, the application of lidocaine does not reduce action potential duration, nor does it alter $a_{na}$. In this second group of results, however, there is no action of the drug on the “transient depolarization,” nor is there a reduction in extrasystoles. This second class of results usually occurs in preparations that are more severely depolarized or are “more intoxicated” by the strophanthidin treatment. Many of these experiments have been carried out with very large concentrations of lidocaine (e.g., up to 200 $\mu$M). The fact that the transient depolarization is not reduced under these conditions—even with a concentration of the drug 10 times greater than therapeutic levels—suggests that lidocaine’s action to abolish ectopy does not depend heavily on its actions on mechanisms that do not involve $I_{Na}$. This suggestion is supported by experiments of Eisner et al. (1983a) which indicate that when voltage clamp depolarizations are fixed in duration and the addi-
Elevated $a_{Na}$ and Twitch Tension

We have shown in voltage clamp experiments which control the period of depolarization, that very small changes of $a_{Na}$ can produce significant changes of twitch tension (Eisner et al., 1983c, 1984). This dependence of tension on sodium reflects the power-function dependence of tension on $a_{Na}$ described in Equation 1 and shown in Figure 2. Thus, over the normal range of intracellular sodium, small changes in $a_{Na}$ brought about by changes in rate (e.g., Lederer and Sheu, 1983) or by the application of sodium channel blockers like lidocaine can significantly alter tension. However, when intracellular sodium is elevated significantly above the normal level, a calcium-overload state develops which leads to a complicated dependence of tension on intracellular sodium and calcium (cf. Kort and Lakatta, 1984; Cannell et al., 1985). For example, as intracellular sodium rises during the calcium overload, twitch tension may decline as $I_{T}$ and the aftercontraction are increasing (see Eisner and Lederer, 1979b; Vassalle and Lin, 1979; Bhattacharyya and Vassalle, 1981; Eisner et al., 1984). The alteration in twitch tension behavior when $a_{Na}$ is elevated and calcium overload is present has been attributed to spatially asynchronous intracellular calcium oscillations (Cannell et al., 1985) to reduced sarcoplasmic calcium release (Kort and Lakatta, 1984) and, possibly, to intracellular acidification (Wier and Hess, 1984) that is known to occur under these conditions (Deitmer and Ellis, 1980b; Vaughan-Jones et al., 1983). It is exactly that same calcium-overload state that is responsible for the development of the arrhythmogenic $I_{T}$ (Kass et al., 1978a). Consequently, although we have investigated $I_{T}$ during the period of highly elevated $a_{Na}$ and $a_{Ca}$ and examined the actions of lidocaine, we have not undertaken analysis of the twitch tension under these circumstances in this paper.

Action Potential Duration, Twitch Tension, and $I_{T}$

In this study, we do not attempt to investigate the mechanism whereby the alterations of action potential duration are linked to alterations of twitch tension or alterations of $I_{T}$ magnitude. Instead, we are able to examine phenomenologically the separate effects of changes in action potential duration from the effects of changes of $a_{Na}$. There are at least two distinct mechanisms that may link a shorter action potential to reduced twitch tension and $I_{T}$. (1) Decreased trigger: Shorter action potentials may lead to less calcium release from the sarcoplasmic reticulum. Thus, a specific action potential could have an effect on the subsequent $I_{T}$ and its underlying phasic rise of $a_{Na}$. However, a specific action potential could have only a secondary effect on twitch tension, since the primary phasic rise of calcium that produces the twitch occurs early in the action potential (cf. Wier and Hess, 1984) and would not be altered by the subsequent duration of the action potential. (2) Decreased calcium loading: Shorter action potentials may lead to less net calcium entry via the sarcolemma. A voltage-dependent Na$^{+}$-Ca$^{++}$ exchange mechanism may lead to greater net calcium entry at more positive potentials (cf. Eisner et al., 1983b). Additionally, to the extent that calcium channels do not completely inactivate, shorter depolarizations will contribute to less net calcium entry during shorter action potentials. With this mechanism, like (1) above, a specific action potential can have an immediate action on $I_{T}$ (since it follows the action potential) and affect only a later twitch (triggered by the subsequent action potential). Thus, both possible mechanisms suggest that lidocaine’s shortening of action potential duration would have very rapid actions on $I_{T}$ and a possible action on twitch tension that must be delayed by an interval equal to 1/heart rate. The possible additional actions that alterations of action potential duration have on $a_{Na}$ are addressed below.

Many other workers have examined action potential duration and tension (e.g., Boyett and Fedida, 1984), but, generally, they have not accounted for the possible importance that changes in intracellular sodium may have in modulating tension. Others who also carry out action potential experiments (e.g., Vassalle and Lee, 1984; Im and Lee, 1984), have stressed the importance of $a_{Na}$, without adequately accounting for the importance of changes of action potential duration. Thus, the fall of tension at a constant $a_{Na}$ seen by Vassalle and Lee (1984) when they applied the sodium channel blocker, TTX, has been observed in our experiments when we applied lidocaine (cf. our Fig. 2). In our experiments, the rapid fall in tension with $a_{Na}$ constant is associated with reductions in action potential duration. The dependence of twitch tension on $a_{Na}$ is given by the exponent, N, in our Equation 1. The extremely steep dependence of twitch tension on $a_{Na}$ seen in action potential experiments (our Fig. 1C, filled circles) or in the figures shown in Im and Lee (1984) may reflect the combined actions of changes in action potential duration and changes in $a_{Na}$ that can be seen. In voltage clamp experiments, the value of N in Equation 1 appears to be less (e.g., 3.2 in Eisner et al., 1984) than it is in action potential experiments (e.g., our Fig. 1C, filled circles, where N = 7.9, or in the experiments of Im and Lee (1984), where N = 6.6 in TTX experiments). In Figure 2B (filled circles), the value of N was less than it was in other action potential experiments (N = 4.3) and the changes in twitch tension in this experiment were relatively uncontaminated by changes of action potential duration (see Results). The experiments of Im and Lee (1984) were done on a different animal.
reduce action potential duration. These additional released from the sarcoplasmic reticulum.
calium entry across the sarcolemma and on calcium
pential (i.e., action potential duration) has on net cal-
ctions result from the effects that membrane poten-
et al., 1978a), should have added efficacy if they
clude, therefore, that the shortening of action poten-
The influence of depolarization duration per se in
development of tension is less certain. Fozzard
show that it is clearly important in sheep Purkinje fibers for short action potentials (e.g., less than 50 msec). In more complete experiments, Gibbons and Fozzard (1975) showed how longer depolarizing voltage clamp pulses increased twitch tension in sheep Purkinje fibers. (For ventricular muscle, see similar results in Morad and Trautwein [1968].) In the experiments described by Gibbons and Fozzard, the tension increased over the entire range of depolarization duration tested (up to 1000 msec). Although they did not control changes in $a_{Na}$, their findings appear valid nevertheless. Note that increasing the depolarizing pulse duration may decrease $a_{Na}$ in sheep Purkinje fibers (Fig. 5, this paper, and cf. Eisner et al., 1981, 1982, 1983b; January and Fozzard, 1984). If $a_{Na}$ had decreased, its action on tension would be to decrease it rather than to increase it (the observed action). We conclude, therefore, that the shortening of action potential duration produced by a local anesthetic like lidocaine or TTX is an important factor leading to the observed decrease in twitch tension.

Implications for Other Antiarrhythmic and Negative Inotropic Agents

Calcium Channel Blockers

Calcium channel blockers, in addition to reducing $I_{Na}$ and twitch by reducing calcium "load" (cf. Kass et al., 1978a), should have added efficacy if they reduce action potential duration. These additional actions result from the effects that membrane potential (i.e., action potential duration) has on net calcium entry across the sarcolemma and on calcium released from the sarcoplasmic reticulum.

Other Antiarrhythmic Agents

The results of the experiments presented in this paper imply that, in addition to other immediate actions that may result from the application of an antiarrhythmic agent, $I_{Na}$-dependent arrhythmias should be immediately improved as the agent shortens the action potentials, or immediately enhanced as the agent lengthens the action potential. The steady state actions of the antiarrhythmic agents on $I_{Na}$ will depend on the slower acting modes of action, as well. Thus, quinidine, for example, long known to produce severe cardiac arrhythmias as a rare (3%) side effect (Selzer and Wray, 1964), may do so in part because quinidine can prolong the action potential of cardiac tissue (e.g., Colatsky, 1982) and thereby potentiate any pre-existing $I_{Na}$. Since quinidine reduces the repolarizing potassium current $I_{K}$ in addition to reducing $I_{Na}$ (cf. Colatsky, 1982), when a prolongation of the action potential is observed, it presumably suggests that quinidine’s effect on $I_{K}$ was greater than its effect on $I_{Na}$. Nevertheless, in the steady state, at least, quinidine reduces the magnitude of the transient depolarization (Wasserstrom and Ferrier, 1982). This may reflect the steady state reduction of $I_{Na}$ and, consequently, of $a_{Na}$, although this has not been demonstrated experimentally. Furthermore, the relationship between action potential duration changes produced by quinidine and alterations in both $I_{Na}$ magnitude and $a_{Na}$ must be determined, as well. Finally, it is worth noting that we are not suggesting that the additional actions of various antiarrhythmic agents (such as the action of tetracaine to block calcium release by the sarcoplasmic reticulum) are unimportant. Instead, we point out how alterations of action potential duration (and $a_{Na}$ and $a_{Ca}$) may be important additional features to consider when investigating the cellular basis of action of the various antiarrhythmic agents.

Use-Dependence: Implications

Bean et al. (1983) have demonstrated that lidocaine acts in a use-dependent manner. Repetitive depolarizations promote a greater degree of blockade by a fixed concentration of lidocaine over the therapeutic range. They showed furthermore that lidocaine binds to the sodium channel when it was inactivated. The consequence of these results is that, when the heart rate increases or when the action potential duration gets longer or when the fraction of time the cardiac cells are depolarized becomes greater, lidocaine’s block of sodium channels will increase (other factors being equal). The actions of a given concentration of lidocaine will be more potent because of use dependence. Lidocaine will consequently decrease excitability, shorten the action potential duration, reduce twitch tension, reduce $I_{Na}$-dependent arrhythmias and decrease $a_{Na}$ more effectively that it would had use dependence not been a factor.
Sheu and Lederer/ Mechanism of Action of Lidocaine

Reentrant Arrhythmias vs. "Triggered" Arrhythmias

This report suggests that whenever lidocaine (or other agent) blocks sodium channels, it can antagonize the development of \( I_{Na} \) and thereby block or reverse this membrane current responsible for "triggered" arrhythmias. Similarly, however, lidocaine's blockade of sodium channels leads to a reduction of excitability and can thereby abolish reentrant excitation by converting a region of unidirectional blockade into a region of complete conduction block. The overall efficacy of lidocaine and other sodium channel blockers would appear to be enhanced by their ability to block both kinds of arrhythmia.

Conclusions

We conclude that lidocaine acts as an antiarrhythmic drug and a negative inotropic agent by blocking sodium channels. Lidocaine’s action on sodium channels brings about an immediate reduction of “excitability” and is also responsible for the shortening of the action potential. These effects can explain the immediate fall in twitch tension and the reversal of certain arrhythmias (dependent on \( I_{Na} \) and the transient depolarization). Secondarily, reduction of \( a_{Na} \) leads to additional reduction of tension and of the arrhythmogenic current \( I_{Na} \). The secondary effects are mediated by a fall in \( a_{Na} \) due to the Na\(^+\)-Ca\(^+\) exchange mechanism.

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Lidocaine's negative inotropic and antiarrhythmic actions. Dependence on shortening of action potential duration and reduction of intracellular sodium activity.

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