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Cardiac instability amplified by use-dependent Na channel blockade

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Starmer, C. Frank, Alisa R. Lancaster, Anselmo A. Lastra, and Augustus O. Grant. Cardiac instability amplified by use-dependent Na channel blockade. *Am. J. Physiol.* 262 (*Heart Circ. Physiol.* 31): H1305–H1310, 1992.—Drugs that exhibit use-dependent Na channel blockade, including antiarrhythmic agents, tricyclic antidepressants, opiate-like analgesics, and cocaine, are linked with an increased susceptibility to cardiac arrhythmias and sudden death. Computer simulations indicate that Na channel blockade retards recovery of excitability, thereby increasing the spatial dispersion of refractoriness, a precursor of many cardiac arrhythmias. In isolated rabbit left atria, stimuli timed to occur at increasing intervals following conditioning stimuli reveal an unstable interval (vulnerable period) during which single stimuli initiate trains of responses. The vulnerable period is extended by use-dependent Na channel blockade and provides a model for assaying proarrhythmic potential and probing cardiac instability.

ion-channel; local anesthetic; cocaine; propoxyphene; lidocaine; arrhythmia; proarrhythmia; abused substance

SUDDEN DEATH often follows cardiac rhythm disturbances that are initiated by excitation of electrically unstable tissue. A hallmark of unstable tissue is that electrical excitability is spatially heterogeneous such that single stimuli can initiate trains of responses (20, 28). A stimulus applied early during the cardiac cycle encounters absolutely refractory tissue and evokes no response [1:0 stimulus-response (s-r) coupling], whereas a stimulus applied late during the cardiac cycle exhibits 1:1 s-r coupling. However, between these two extremes is a vulnerable period (VP) (1, 20, 28) paralleling late repolarization during phase 3 of the action potential during which responses to single stimuli deviate from these patterns and may elicit repeated activation in the absence of additional stimuli (1:many s-r coupling). Consequently, interventions that extend the VP can be defined as proarrhythmic and can lead to life-threatening rhythms and sudden death. Although the VP parallels the recovery of Na channel availability, determinants of its boundaries are unclear. Na channels recover from inexcitability during the T wave, and in diseased conditions, T wave alternans has been identified as one important marker of cardiac instability (13, 16, 17, 19). Moreover, use-dependent Na channel antagonists including abused substances such as cocaine (11), propoxyphene (27), tricyclic antidepressants (25), as well as many antiarrhythmic agents (15, 26) appear to amplify cardiac instability. How can single Na channel events influence the collective stability of intact tissue?

In most neuronal and cardiac cells, Na channels provide the ionic current required to initiate and sustain a propagating action potential. Consequently, we can approximate excitability with the fraction of Na channels available to conduct at any time. Na channels respond to changes in membrane potential, switching between nonconducting and conducting states. Switching between channel states represents an inherent nonlinear response, and as the switching event propagates, cell states become spatially inhomogeneous, thus providing a basis for cardiac instability. In these studies, we examine the linkage between the use-dependent properties of many Na channel antagonists, their time-dependent modulation of the recovery of excitability, and the propagation of an activation wavefront in intact cardiac tissue.

In contrast to ligands that have continuous access to receptor binding sites, many antiarrhythmic drugs and abused substances block Na channels in a use-dependent manner (2, 3, 6, 9, 11, 15, 25–27) and can be readily modeled by considering binding-site access to be dependent on membrane potential or channel agonists (23). Often, formation of nonconducting drug-complexed channels is dominant for depolarized (excited) conformations paralleling the open or inactivated states, whereas unbinding is dominant when channels are in the rest conformation at a polarized potential. Drug-complexed channels mimic channel inactivation by rendering the channel nonconducting, and unbinding prolongs the return of channels to the rest state, thereby amplifying the time during which cardiac tissue is unstable. Thus, during a cardiac cycle, the fraction of drug-complexed channels (and excitability) varies in response to the cyclic changes in channel conformation and the kinetics of the drug-channel interaction.

In an intact preparation, the spatial dispersion of cell states reflects both the coupling of excitation from cell to cell and the time a channel spends in transition between states. Studies of s-r coupling in cardiac tissue using pulse train stimulation have yielded an interesting nonlinear model of blocked excitation in which s stimuli evoke r<s responses (Wenckebach rhythms) and in which the pattern of blocked responses is sensitive to

initial conditions as determined by the stimulus frequency (5, 18). Short recovery intervals are associated with longer intervals coupling a stimulus with a response than are long recovery intervals. These models predict many clinically observed arrhythmias derived from stimulation intervals that are shorter than the time course of complete cellular recovery of excitability. With short interstimulus intervals, each stimulus will occur progressively earlier during the recovery phase initiated by the prior stimulus, thereby encountering progressively fewer recovered cells until refractoriness is encountered. Although these studies were limited to one-dimensional propagation, they suggest the possibility of stimulus-multiplying arrhythmias, i.e., 1:many s-r coupling, when the recovery properties are anisotropic (20).

This view can be generalized to include the effects of use-dependent channel blockade. As a wavefront of cellular excitation propagates, retarded recovery of excitability within the wake of the propagating wavefront prolongs the time during which cell states are disparate, thus hypothetically amplifying the substrate for arrhythmic responses (22, 24). Drugs that unbind rapidly, such as lidocaine (unbinding time constant = 200 ms) (8), are inherently less proarrhythmic than drugs such as flecainide, cocaine, and propoxyphene, which exhibit unbinding time constants > 5 s (3, 6, 27). These studies were designed to explore the interaction between stimulus timing and the drug-induced modifications of excitability using use-dependent Na channel antagonists that exhibited a range of unbinding time constants.

METHODS

Hearts were carefully removed from 2.5- to 3-kg rabbits anesthetized with ketamine (5–10 mg/kg im) and pentobarbital sodium (40–70 mg/kg ip) and placed in room temperature Tyrode solution of the following composition (in mM): 127 NaCl, 2.7 KCl, 22 $NaHCO_3$, 0.5 NaH_2PO_4, 0.5 $MgCl_2$, 1.8 $CaCl_2$, and 5.5 dextrose. The solution was oxygenated with a mixture of 95% O_2-5% CO_2. The left atrium was carefully dissected from the heart and pinned to the Silastic bottom of a 20-ml study chamber. Solutions were warmed to 35°C and passed through the chamber at a rate of 20 ml/min. Bipolar tungsten stimulation electrodes were placed near the center of the epicardial surface of the atrium. A unipolar Ag-AgCl electrode was placed near the perimeter of the atria. Unipolar electrograms were amplified and recorded on magnetic tape for later analysis. Stimulation was performed using a microcomputer (IBM/XT) and a Labmaster A/D interface. The preparation was stimulated at a 2-Hz rate at ×5 threshold for 1 h before any measurements were made. We investigated the electrical responses to premature stimulation using a train of 10 pulses (s_1) followed by a single premature stimulus (s_2). We manipulated the initial conditions by varying the delay between the last s_1 "drive" pulse and the s_2 "premature" pulse. We set the delay to a value less than the expected refractory period and then, using the s_1 train followed by the s_2 premature stimulus, tested for a response. The delay was incremented by 1 or 2 ms, and the procedure was repeated. Sometimes the procedure was reversed and the delay was initially set to a large value and decremented by 2-ms increments. We varied the fraction of blocked channels by using s_1 stimulation frequencies of 1 Hz and 2 Hz. After we determined the control VP, the preparation was exposed to the drug-Tyrode solution for 20 min, and we determined the VP boundaries. This was followed by 30 min of washout after which we again scanned the interstimulus interval for the VP.

RESULTS

In drug-free superfused left atria of rabbit, critically timed s_2 stimuli occasionally evoked 1:many responses, but more often the VP was not detected (VP = 0 ms), yielding a mean VP duration of 0 ± 0 ms (mean ± SD, n = 11). When a 1:many response was initiated, it always terminated spontaneously and was never longer than three successive activations. Addition of a slowly unbinding Na channel antagonist to the superfusate always unmasked a critical range (VP) of stimulus delays during which we found 1:many s-r coupling (Fig. 1, *A-C*). The 1:many response trains almost always spontaneously terminated. Slowly unbinding propoxyphene (2 μM) extended the VP to 15 ± 8 ms ($P < 0.01$, $n = 6$). After 30 min of washout with drug-free Tyrode solution, the VP returned to 0 ms. Moreover, if a window was observed with drug-free solutions, then the addition of drug always prolonged its duration as well as the number of activations within the train. The nature of the 1:many response was also frequency dependent. When the drive frequency was reduced from 2 to 1 Hz, the number of repetitive responses within a train was reduced (Fig. 1, *D-F*).

Analysis of successive interactivation (A-A) intervals within a response train revealed a general pattern of progressive prolongation of the coupling interval between successive activations. Early A-A intervals were short, followed by a gradual extension of the A-A interval. During the terminal phase of the response train, the A-A intervals oscillated between long and short intervals (Fig. 2). In addition, the A-A intervals derived from a train initiated by the shortest s_1-s_2 delay within the VP were consistently less than the A-A intervals derived from a train initiated by the longest s_1-s_2 delay within the VP, indicating that the trajectories followed by the activation process were quite sensitive to the initial conditions determined by the s_1-s_2 delay.

Cocaine [unbinding time constant = 8.5 s (7)] prolonged the VP as shown in Fig. 3. However, the reactivation was frequently maintained until the next s_1 train was initiated. In the absence of drug, the control VP was 0 ± 1 ms ($n = 6$). After a 20-min exposure to 3 μM cocaine, the VP was extended to 22 ± 12 ms ($P < 0.01$; $n = 6$). After 30 min of washout, the VP could not be detected. For cocaine, the 1:many response trains rarely spontaneously terminated but were terminated by stimuli in the next s_1 drive train.

Rapidly unbinding lidocaine unmasked a much smaller VP (Fig. 4). Exposure to 42 μM lidocaine produced a negligible extension of the VP from 0 ± 0 ms to 1 ± 1 ms ($P > 0.1$; $n = 4$). In all cases, reduction in the s_1 drive rate resulted in shorter response trains within the VP, and for lidocaine, the VP could not be detected with a 1-Hz s_1 stimulation rate.

DISCUSSION

Proarrhythmic complications are frequently associated with both antiarrhythmic drugs and many abused substances including cocaine, propoxyphene, and the tricyclic antidepressants. All these drugs have as a common denominator the use-dependent blockade of cardiac

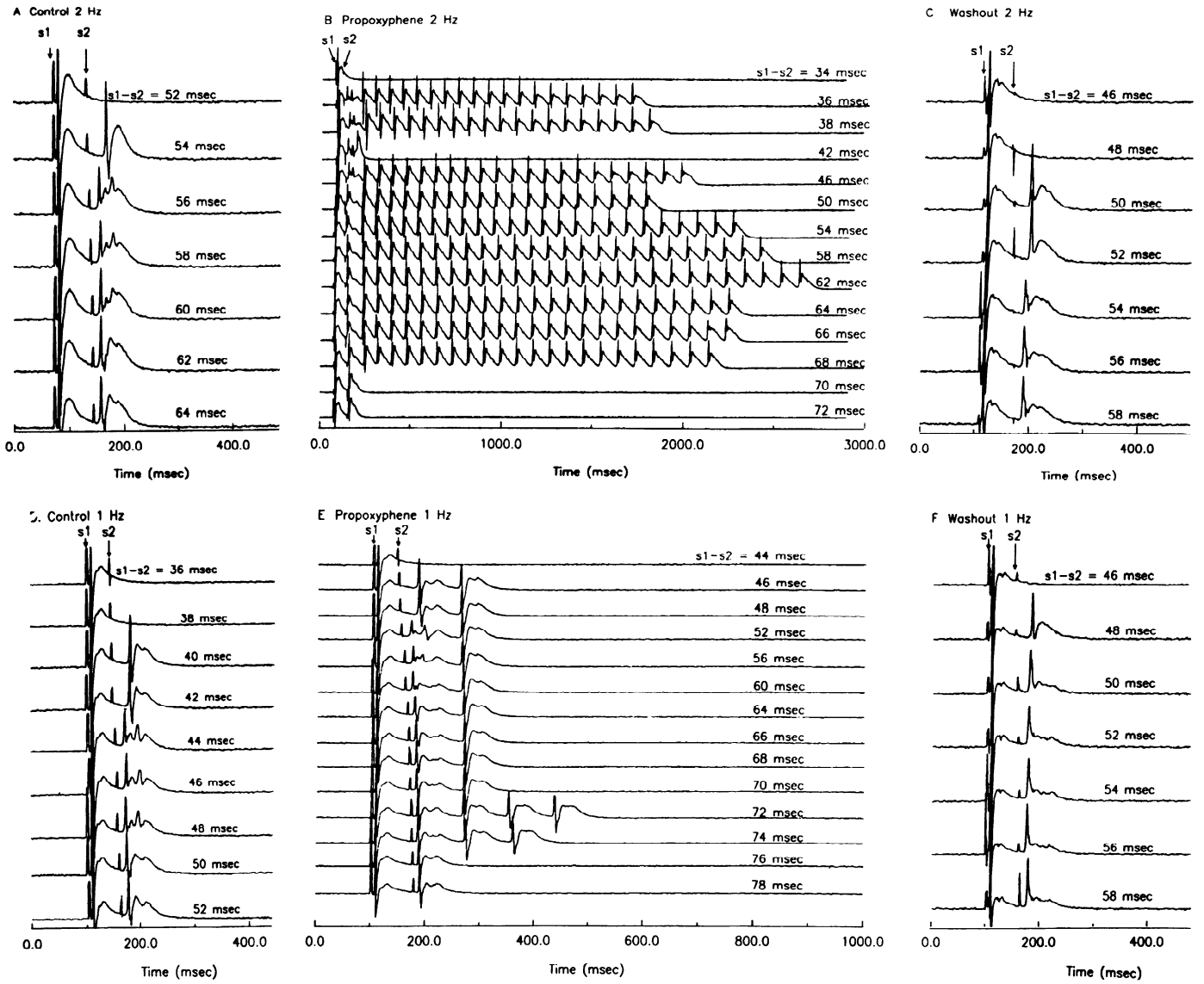

Fig. 1. Typical sequence of responses to premature stimulation under drug-free conditions and in presence of 2 μM propoxyphene at stimulation rates of 1 (*bottom*) and 2 Hz (*top*). Shown are stimulus artifacts (low-amplitude spikes before large electrical responses) and responses for last stimulus in train, and response (if any) to a single premature stimulus. Under control conditions (*A, D*), we always found a range of delays during which there was no s_2 response (1:0 coupling) corresponding to classical refractory period. Progressively increasing the delay, we sometimes found delay during which s_2 evoked 1 or more responses. In this preparation, continuing to increase delay exposed another transition point where responses reverted from 1:many coupling to 1:1 coupling. Adding a slowly unbinding use-dependent Na channel antagonist to superfusate always produced vulnerable period (VP; *B, E*). Switching to drug-free perfusate for 30 min reversed effect (*C, F*). Although VP duration was relatively insensitive to drive stimulus rate, pattern of responses within VP was clearly frequency sensitive. At 1-Hz stimulation rate, number of repetitive responses was always less than at 2-Hz rate.

Na channels. We hypothesized that slowing the recovery of Na channel availability might be associated with an amplification of proarrhythmic (1:many s-r coupling) responses by increasing the time during which Na channel availability was spatially nonuniform. This hypothesis was initially explored with numerical studies of a computer model of the drug-channel interaction during the course of an action potential (22). In these studies we showed increased vulnerability to premature stimulation in the presence of use-dependent Na channel blockade.

Allessie and colleagues (1) found reentrant activation could be initiated and a VP identified in rabbit left atria. Using the same preparation, we found that prolonging the recovery of Na channel availability in vitro with use-dependent drugs extended the VP and that the degree of extension was sensitive to the drug-unbinding rate. Thus use-dependent Na channel blockade increases the instability of cardiac tissue with respect to premature stimulation.

It is possible to approximate the degree of instability by exploring the effect of Na channel blockade on the propagation velocity Θ of an excitation wavefront (12, 14, 15). The mass of unstable tissue undergoing recovery during the vulnerable period must be proportional to $\Theta\tau$, where τ is the drug-unbinding time constant. Whereas

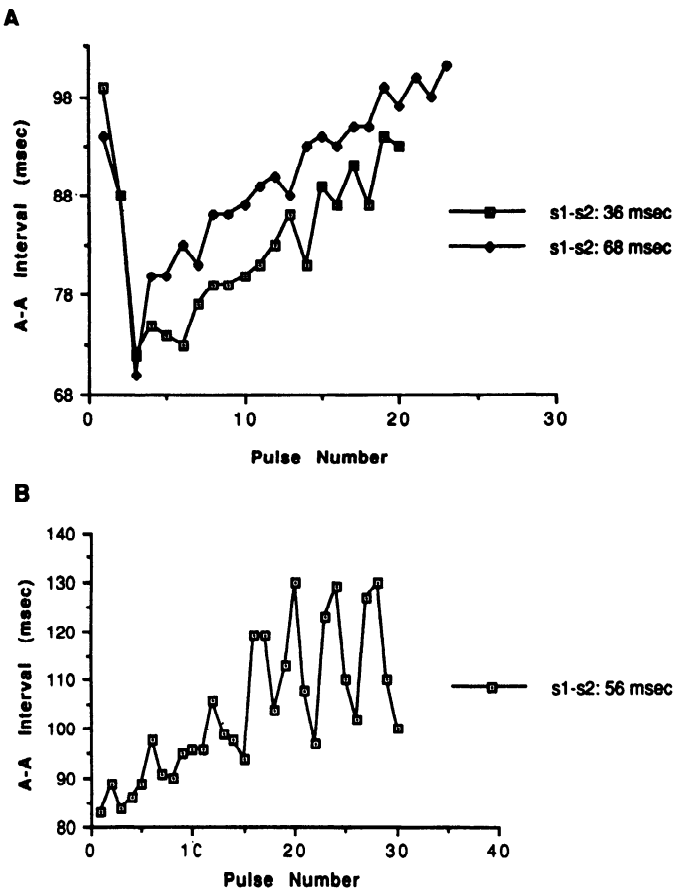

Fig. 2. Time interval between successive activations of trains induced by premature stimuli within VP displayed consistent pattern. After short sequence of activations (1–3), there was gradual prolongation of interval between successive activations. Just before self-termination of sequence of activations, interactivation (A-A) interval began to oscillate between short coupling intervals and long coupling intervals. *A*: plot of A-A interval derived from response trains illustrated in Fig. 1. Two traces represent A-A intervals from trains initiated with premature stimuli placed at most and least premature boundaries of VP. Note that pattern of A-A intervals showed no overlap once initial transient response was over. *B*: example derived from another study that illustrates extreme oscillation in A-A intervals just before self-termination.

Θ may be reduced as much as 50–75% in the presence of channel blockade (12, 14), unbinding time constants can differ by a factor of 100 (26), leading to net increase in $\Theta\tau$ and consequently an increase in the mass of unstable tissue with slowly unbinding use-dependent agents.

Instability can be further modulated by heart rate in conjunction with use-dependent drugs. Increasing the heart rate increases the availability of use-dependent drug binding sites and promotes the formation of drug-complexed channels (6, 7, 27). In our studies, we found the temporal pattern of the 1:many responses was sensitive to the s_1 stimulation rate. Longer response trains (Fig. 1*B*) were observed with 2-Hz stimulation than with 1-Hz stimulation (Fig. 1*E*). These observations are consistent with slowed conduction secondary to increased steady-state block derived from the diminished time available for unblocking at 2 Hz. Slowed conduction should hypothetically reduce the likelihood of a propagating action potential encountering refractory tissue left in the wake of its predecessor, thus promoting longer response trains.

Why is it interesting to identify modulators of cardiac instability? Recently, we found that the electrophysiological correlates of cardiac toxicity in the setting of propoxyphene abuse could be reversed by lidocaine (27). Cellular studies showed both lidocaine (unbinding time constant ~2 s at 15°C) and propoxyphene (unbinding time constant ~20 s at 15°C) to be use-dependent Na channel antagonists. Unlike ligands with continuous binding site access, in which competition leads to an increased fraction of drug-complexed channels, competition between two use-dependent channel antagonists can result in a paradoxical reduction in the steady-state fraction of blockade and a reduction in the apparent unbinding time constant (21, 27), leading to a reduction in unstable mass and a reversal of cardiotoxic effects. Consequently, these initial studies provide a general framework not only for probing the determinants of electrical instability of excitable tissue but also for probing protocols for reversing some of these effects.

Perhaps more importantly, arrhythmia management based on suppression of premature ventricular contractions (PVCs) with use-dependent Na channel antagonists appears to be inherently proarrhythmic. In fact, unsuppressed PVCs in the presence of Na channel antagonism may be more malignant than unsuppressed PVCs in the absence of Na channel antagonism (4).

These studies have provided an interesting basis for exploring "scaling" of molecular events (drug-channel binding) to macroscopic behavior (patterns of electrical activation of a large collection of interconnected cells). Studies of single-channel events in the presence and absence of drug provide an incomplete picture of events derived from the intact heart (8). Scaling of single-channel currents to whole cell currents is linear and predictable. When the conduction velocity is slow relative to the state transitions of a channel, adjoining cells will exhibit different degrees of Na channel availability such that extrapolation of single-cell responses to multiple cells will be inherently nonlinear. Consequently, multicellular responses can be difficult to predict. These studies suggest how the collective properties (derived from activation propagating from cell to cell) diverge from individual cellular properties and how nonlinear cellular properties coupled with propagation can lead to instabilities. Moreover, these studies demonstrate the nonlinear nature of cardiac excitability, as reflected by responses that exhibit sensitivity to initial (s_1-s_2 delays) conditions.

Most class 1 antiarrhythmic agents are not pure use-dependent Na channel antagonists but also block potassium and/or calcium channels. Theoretical studies show that use-dependent Na channel blockers are inherently proarrhythmic (22) and that the VP is correlated with the unbinding time constant of the drug. Although the results reported here are in qualitative agreement with this hypothesis [VP(lidocaine) < VP(cocaine); VP(lidocaine) < VP(propoxyphene)], these three agents also block other channels. Consequently, additional studies are required to explore the modulating influence of parallel antagonism of potassium or calcium channels on the VP duration. Our results indicate that a wide class of frequently used substances, including antiarrhythm-

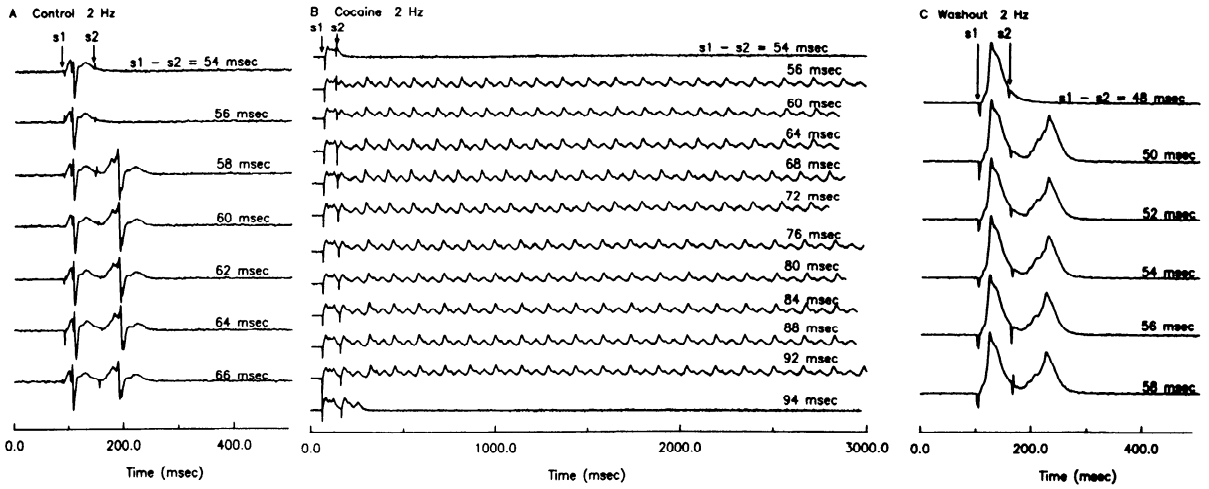

Fig. 3. In studies of cocaine, 4 of 5 preparations exhibited no VP under control conditions or after washout. *A*: typical response to premature stimulation in which no control VP was detected. *B*: progressive delay of s_2 stimulus revealed 36-ms VP. Repetitive response continued for 3 s and was terminated during next pulse train (s_1). *C*: after 30 min of washout, VP could not be detected.

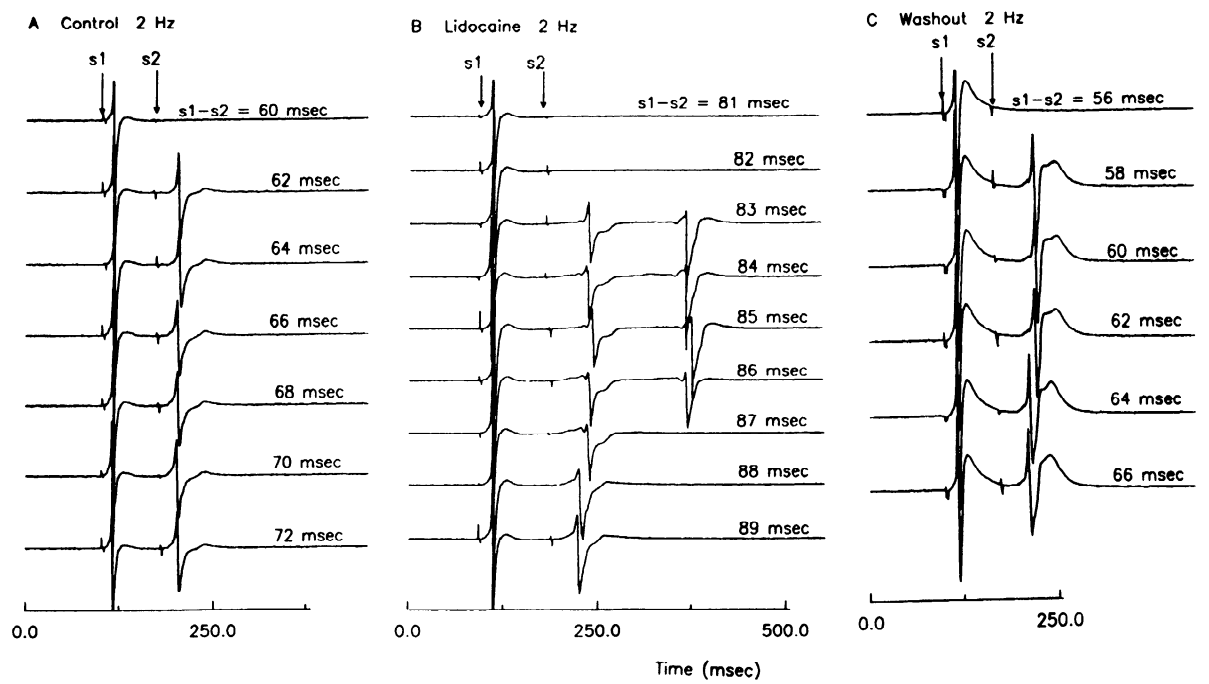

Fig. 4. Rapidly unbinding lidocaine (42 μM) produced negligible effect on duration of vulnerable window. *A*: shows critical transition delay between 1:0 and 1:1 responses in typical preparation and absence of VP. After 20 min of exposure to lidocaine (*B*), 4-ms VP was unmasked. After 30 min of exposure to control solution, period was no longer detectable at 1-ms precision. In 4 experiments, control VP was 0 ± 0 ms, whereas in presence of lidocaine it was 1 ± 1 ms ($P > 0.1$). *C*: after 30 min of washout, VP was undetectable.

ics, local anesthetics, and tricyclic antidepressants, may be inherently proarrhythmic and that additional studies will be necessary to explore other modulators of the vulnerable period.

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