Anesthesiology
64:501–503, 1986

Lidocaine Depresses Synaptic Activity in the Rat Hippocampal Slice

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The direct effect of the local anesthetic lidocaine was studied using the hippocampal slice preparation in order to assess the involvement of this structure in lidocaine-induced seizure activity. Changes in the evoked field potential amplitude and latency were used to measure the effect of the drug. A dose-dependent depression of the evoked field potentials was observed at lidocaine concentration of 10^{-4} M and greater. No synchronized population bursting (seizures) was observed at any of the concentrations tested (10^{-6} M to 10^{-3} M). However, the hippocampal slice preparation is capable of producing seizure activity, as was demonstrated following application of penicillin G. The results suggest that the hippocampus is not the site of lidocaine-induced seizure activity. (Key words: Anesthetics, local: lidocaine. Brain: convulsions; hippocampus. Toxicity: lidocaine.)

LIDOCAINE, WHEN ADMINISTERED at doses in excess of 6–12 mg/kg iv, may produce seizure discharges.[1,2] Both the amygdala and the hippocampus have been implicated as the primary sites of lidocaine-induced seizure activity,[2] although the precise locus remains controversial.[3] The hippocampal slice preparation is ideal for the study of synchronized population bursting seen in the presence of gamma-aminobutyric acid (GABA)-ergic blockers such as penicillin,[4,5] This event resembles the interictal spikes recorded in the cat hippocampus after the application of penicillin. Interictal spikes can be compared directly to those observed in human epileptic patients.[4] GABA appears to be the major inhibitory neurotransmitter in the hippocampus,[4] and diazepam, the GABA-facilitator, has been shown to be effective in the prevention of lidocaine-induced convulsions *in vivo*.[3,6,7] Based on these considerations, the hippocampal slice preparation was used in the present study to determine the direct effect of graded doses of lidocaine on this structure.

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Received from the Anesthesia and Critical Care Research Unit (ACCRU), Department of Anesthesiology and Department of Physiology and Biophysics, University of Louisville, School of Medicine, Louisville, Kentucky 40292. Accepted for publication November 19, 1985.

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Methods

Tissue Preparation and Maintenance

Adult male Sprague-Dawley rats (300–500 g) were decapitated, and their brains were removed within 2 min, rinsed with cold (5–10° C) oxygenated artificial cerebrospinal fluid (ACSF),[8] and dissected. Isolated hippocampi were sectioned transversely at 400 μm with a tissue chopper and placed in a linear flow recording chamber.[9] In each experiment, 5–6 slices from the same hippocampus were placed in the chamber. They were supported on a nylon mesh and superfused with ACSF at 40 ml/h. A humidified gas mixture (1 l/min) of 95% O_2/5% CO_2 was circulated over the slices. The chamber was maintained at 34 ± 0.5° C.

Measurements

Extracellular recordings of orthodromically evoked population field potentials (population spike) from stratum pyramidale of the CA1 region were made from one slice using a borosilicate micropipette filled with ACSF. The impedence of the recording glass microelectrode never exceeded 5 MΩ. Signals were amplified (×100), displayed on an oscilloscope, digitized, and stored on a floppy disk for later analysis.[8] A bipolar stainless steel stimulating electrode with tips 200 μm apart was placed through the full thickness of the slice, in the region of the Schaffer collaterals of the stratum radiatum near CA1. Isolated stimulus pulses were 0.1 ms in duration and of an amplitude twice the threshold, which was typically under 5 V. CA1 responses were recorded automatically. A waveform analysis program was used to determine population spike latency and amplitude[9] (fig. 1).

Experimental Design

CA1 population responses were recorded every minute starting 2 h after decapitation. After the 30-min control period, lidocaine (10^{-6} M to 10^{-3} M), or penicillin G

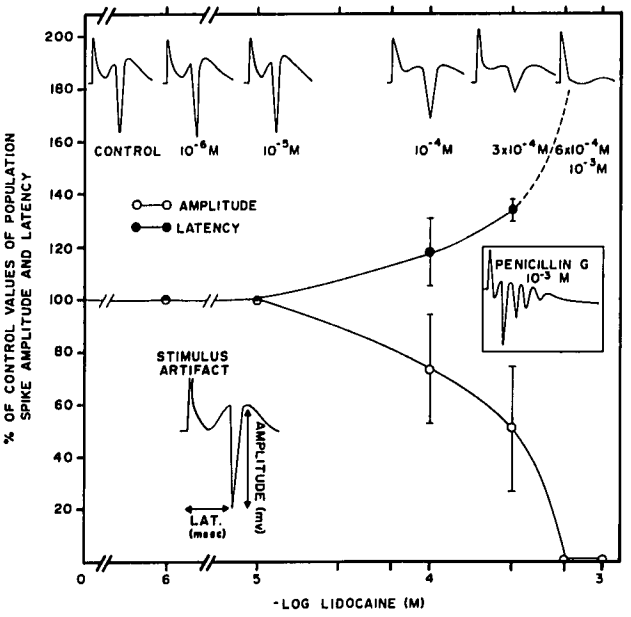

FIG. 1. Dose-dependent changes in the amplitude (O) and latency (●) of the population spike evoked in rat hippocampal slices after 1-h application of lidocaine as compared with control activity before drug administration. Also shown are the variables measured (*bottom, left*) and representative isolated population responses under different lidocaine concentrations (*top*). While the amplitude of the population spike decreased with increased lidocaine concentration, its latency increased. Bars are mean ± SD (n = 3). A CA1 population response in the presence of 10^{-3} M penicillin G is shown in inset at right.

(10^{-3} M to 10^{-2} M) was perfused *via* the ACSF for a duration of 60 min. At the end of this period the drug solution was replaced by drug-free ACSF, and records were collected for an additional 30 min. Thus, the experiment had a total recording time of 120 min. Each experiment was repeated at least three times, and the results are expressed as mean ± SD.

Results

Lidocaine at doses less than 10^{-4} M affected neither the amplitude nor the latency of the evoked population spike (figs. 1 and 2). At concentrations greater than 10^{-4} M lidocaine elicited depression of synaptic activity. The amplitude of the population spike decreased and totally disappeared at doses of 6×10^{-4} M and greater while its latency was prolonged (fig. 1). Representative evoked responses at different doses of lidocaine are shown at the top of figure 1. On replacing the drug solution with lidocaine-free ACSF, the depressant effect was washed out within 15–20 min (fig 2). When penicillin G was administered at a concentration of 10^{-3} M, synchronized population bursting had occurred (fig. 1, inset), while 10^{-2} M of the drug depressed the evoked synaptic activity.

Discussion

The hippocampus has been implicated as one of the primary sites of lidocaine-induced seizure activity.[2] By using the hippocampal slice preparation, a very useful model in the study of epileptiform activity,[5] we attempted to determine the direct effect of graded doses of lidocaine on this structure. Depsite the wide range of lidocaine concentrations (10^{-6} M–10^{-3} M) used (2×10^{-5} M corresponds to 5 μg/ml plasma or 2 mg/kg body weight, which is the therapeutic dose), only depression of synaptic activity was observed. This effect was produced by lidocaine concentrations of greater than 10^{-4} M, and its duration was directly related to the drug concentration; the greater the concentration, the longer was the duration of its effect. One might question the ability of the hippocampal slice preparation to exhibit synchronized population bursting, which could be the explanation for the inability of lidocaine to induce such activity. However, the ability of penicillin to produce both synchronized population bursting at 10^{-3} M and strong depression at 10^{-2} M demonstrates the capability of this preparation to produce seizure-like activity. Because blockade of GABA-mediated inhibition was suggested as the mechanism for both lidocaine- and penicillin-induced seizure activity,[3,4] our results indicate that this might not be the case for lidocaine, at least where

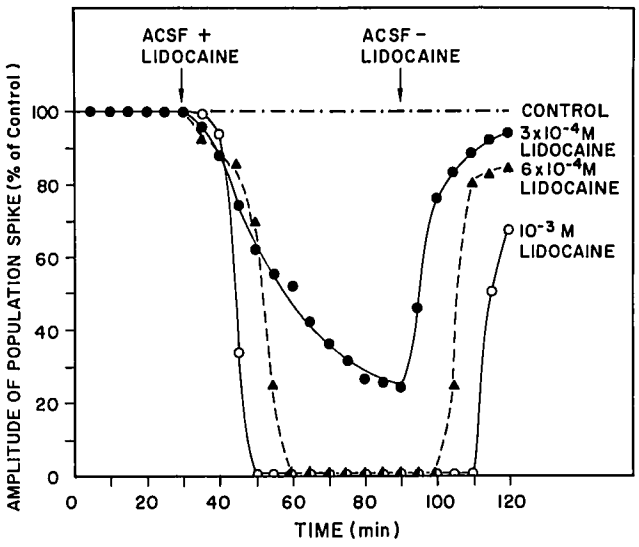

FIG. 2. Representative experiments of time-dependent effects of three different concentrations of lidocaine (3×10^{-4} M = ●; 6×10^{-4} M = ▲; 10^{-3} M = O) on the amplitude of the CA1 population spike evoked in rat hippocampal slices. After 30 min of baseline recording (control), the normal artificial cerebrospinal fluid (ACSF) solution was replaced with ACSF + lidocaine, and the slices were perfused with the drug for 60 min. ACSF without lidocaine was used thereafter to washout the drug for an additional 30 min. The greater was the lidocaine concentration, the more profound and longer was the depression of the evoked population response.

the hippocampus is concerned. It has been shown that the amygdala is the main structure affected by lidocaine *in vivo*.[2,3] It could be that the hippocampus is affected by lidocaine indirectly through the amygdala and, because an afferent input from the latter is absent in our preparation, no seizure activity could be induced by the drug. On the other hand, lidocaine's seizure activity could be mediated through inhibitory modulation from the hippocampus.

In conclusion, our results suggest that the hippocampus is not the primary site of action of lidocaine with respect to seizure activity because the drug depresses synaptic activity in this structure.

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