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Characteristic Intracelluar Response to Lidocaine and MK-801 of Hippocampal Neurons: An *In Vivo* Intracellular Neuron Recording Study

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This study used in vivo intracellular recording in rat hippocampus to evaluate the effect of lidocaine and MK-801 on the membrane properties and the synaptic responses of individual neurons to electrical stimulation of the commissural pathway. Cells in control group typically fired in a tonic discharge mode with an average firing frequency of 2.4±0.9 Hz. Neuron in MK-801 treated group (0.2 mg/kg, i.p.) had an average input resistance of 32.8±5.7 MΩ and a membrane time constant of 7.4±1.8 ms. These neurons exhibited 2.4±0.2 ms spike durations, which were similar to the average spike duration recorded in the neurons of the control group. Slightly less than half of these neurons were firing spontaneously with an average discharge rate of 2.4±1.1 Hz. The average peak amplitude of the AHP following the spikes in these groups was 7.4±0.6 mV with respect to the resting membrane potential. Cells in MK-801 and lidocaine treated group (5 mg/kg, i.c.v.) had an average input resistance of 34.5±6.0 MΩ and an average time constant of 8.0±1.4 ms. The cells were firing spontaneously at an average discharge rate of 0.6±0.4 Hz. Upon depolarization of the membrane by 0.8 nA for 400 ms, all of the tested cells exhibited accommodation of spike discharge. The most common synaptic response contained an EPSP followed by early-IPSP and late-IPSP. Analysis of the voltage dependence revealed that the early-IPSP and late-IPSP were putative Cl^--and K^+-dependent, respectively. Systemic injection of the NMDA receptor blocker, MK-801, did not block synaptic responses to the stimulation of the commissural pathway. No significant modifications of EPSP, early-IPSP, or late-IPSP components were detected in the MK-801 and/or lidocaine treated group. These results suggest that MK-801 and lidocaine manifest their CNS effects through firing pattern of hippocampal pyramidal cells and neural network pattern by changing the synaptic efficacy and cellular membrane properties.

Key Words: Lidocaine, MK-801, Hippocampus, Local anesthetics, Intracellular recording, Commissural pathway

INTRODUCTION

Local anesthetics reversibly block impulse conduction along nerve axons and other excitable membranes that utilize sodium channel as the primary means of action potential generation (Covino, 1986; Butterworth & Strichartz, 1990). None of the currently available local anesthetics are ideal, though efforts to develop newer agents are underway. In comparison with synthesizing a chemical with local anesthetic effects, to reducing the toxicity of a chemical significantly below that of the current agents is far much difficult. It is mainly because the toxicity of local ansethetics extends its therapeutic effects on the brain and the circulatory system (Frank & Sanders, 1963). Serious toxic reactions to local anesthetics are mostly due to convulsions from excessive blood levels.

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So far, effects of local anesthetics on central nervous system has been focused mainly on clinical symtoms and signs that include sleepiness, light-headedness, visual and auditory disturbances, and restlessness (Wagman et al, 1967). Essentially, nothing is known about the relations between the response of single neuronal cell that contain NMDA receptors and convulsive action by local anesthetics. The cellular mechanisms of convulsion have been hypothetized that it is caused by GABAergic synaptic disinhibition, which is attributable the hyperexcitability or glutamatergic hyperexcitability of the pyramidal cells (McNamara, 1994; Dudek & Spitz, 1997). This study evaluated the hypothetical cellular mechanisms responsible for lidocaine-induced convulsion.

Electrophysiologic and behavioral studies in local anesthetics-treated animals have suggested that the convulsion induced by lidocaine might evoke brain damages (Stripling & Hendricks, 1981; Stripling, 1982). Although cytochemical and electrophysiological methods have shown that lesions induced by excitatory amino acids resemble those by convulsants such as pentylentetrazole, strychnine, and tacrin (Turski et al, 1983; Onley, 1986), there remain unanswered questions, such as: whether this action appears with local anesthetics; what the mechanisms of convulsion are; or what the functional role of NMDA receptor is.

One possible mechainsm of brain damage may involve glutamate receptors (Choi et al, 1988). Recently, several types of glutamate receptors were reported exist: such as N-methyl-D-aspartate (NMDA), Kainate/alpha-amino-3-hydroxy-5-methyl-4-isoxazale propanoic acid (KA/AMPA), and metabotropic receptors (Watkins & Evans, 1981; Watkins et al, 1990; Young & Fag, 1990). Since auditory-evoked and amygdala-kindled seizures were suppressed by NMDA antagonist, it was suggested that NMDA receptor might be stimulated by glutamic acid secretion from neuronal ending during convulsion (Chapman & Meldrum, 1989; Sato et al, 1989; Tricklebank et al, 1989; Young et al, 1989). However, KA/AMPA receptor and non-NMDA receptor of glutamic acid also caused brain damage (Mattson et al, 1989). It is not certain which receptor(s) generate these brain damages. In order to evaluate the role of NMDA receptor during convulsion electrical responses of neurons from hippocampus was recorded by injecting MK-801, a noncompetitive NMDA antagonist.

The present study was designed to determine, first, whether local anesthetics have any effects on membrane properties and synaptic responses in hippocampal pyramidal cells and second, whether MK-801 affect electrophysiological responses of local anestheics. To answer these questions, rat hippocampal neurons were studied by using intracellular recording and staining techniques in vivo. Because the responses in these preparations, unlike those in vitro system, do not contain artificial factors, these preparations facilitated the analysis of physioloical responses with intact local network system.

METHODS

Animals and surgery

This study used male Sprague-Dawley rats (200~280 g). The rats were anesthetized with urethane (1.3~1.5 g/kg) and operated in a stereotaxic apparatus. The body temperature of the rat was kept constant (36°C) by a thermoregulation device. Animals to which drugs were given via i.c.v. route were implanted with a guide cannula (22-gauge stainless steel tube) placed in the lateral ventricle (P 0.8 mm from bregma; L 1.5 mm from midline; V 3.0 mm from dura mater). A stylet was inserted in the cannula and remained there at all times except during i.c.v. injection. Hippocampal CA1 pyramidal cells were targeted since these neurons are susceptable to convulsion. The scalp was removed, and a small bone window was drilled above the hippocampus (anteromedial edge at AP = 3.4 and L = 2.5 mm from bregma) for extra- and intracellular recordings. A pair of stimulating electrodes (100 μm each, with 0.5 mm tip separation) was inserted into the left fimbria-fornix (AP = 1.3 mm, L = 1.0 mm, V = 4.8 mm) to stimulate the commissural inputs to give antidromic activation of CA3 cells and then orthodromic activation of CA1 neurons. Extracellular recording electrodes (three 20 μm insulated tungsten wires) were inserted at the medial edge of the bone window and placed into the upper part of hippocampal CA1 pyramidal cell layer. After the intracellular recording electrode was inserted into the brain, the bone window was covered with a mixture of paraffin and paraffin oil in order to prevent drying of the brain and to decrease pulsation. Electrophysiologic recording started about 60 minutes after lidocaine and/or MK-801 administration.

Intracellular studies

Micropipettes for intracellular recording were pulled from 2.0 mm of capillary glass. They were filled with 1M potassium acetate in 50 mM Tris buffer (pH = 7.2), containing 2.5% neurobiotin for intracellular labeling. In vivo electrode impedances varied from 60 to 100 MΩ. Once stable intracellular recordings were obtained and evoked, and passive physiological properties of the cell were determined. Membrane time constant and input resistance were examined by injecting the cell with hyperpolarizing current pulse and measuring membrane potential deflections. The functions of inhibitory interneuron were evaluated by comparing cessation of firing when commissural pathway was stimulated at the repetitive firing condition, which was induced by depolarizing current. Field activity recorded through the extracellular electrode was filtered between 1 Hz and 5 kHz. The intracellular signal from the amplifier (Axoclamp-2B) was digitized both as a DC signal and as a filtered derivative (0.1 Hz to 5 kHz) after further amplification. The direct and amplified intracellular activity and extracellular field/unit were digitized at 3.3 kHz. The data were stored on disks.

After the completion of the physiological data collection, neurobiotin was injected through a bridge circuit (Axoclamp-2B), using 500-ms depolarizing pulses at 2~5 nA at 1 Hz for 10~60 min. Neuronal activity was followed throughout the procedure. After 1~2 h of postinjection survival times, the animals were given an urethane overdose and then perfused intracardially with 100 ml physiological saline, which was followed by 400 ml of 4% paraformaldehyde and 0.2% glutaldehyde dissolved in phosphate-buffered saline (pH = 7.2). The brains were then removed and stored in the fixative solution overnight. 100-μm-thick coronal sections were cut and processed for neurobiotin labeling as described previously (Attila et al, 1995).

Drugs

Lidocaine was obtained from Sigma Cemical Co., and (+)-MK-801 hydrogen maleate was purchased from RBI and administered in saline.

RESULTS

Data presented here were derived from in vivo intracellular recordings obtained from CA1 cells located in the rat hippocampus. Data obtained only from cells that exhibited stable intracellular penetrations were analyzed. Stability was defined as having steady-state membrane potentials more negative than −50 mV and exhibiting action potentials with amplitudes >50 mV. Neuronal responses to stimulation of the commissural pathway were examined. Neurons were recorded throughout the hippocampal CA1 area. In addition, cells were also stained by intracellular injection of neurobiotin after their electrophysiological characterization to localize the site of recordings within the hippocampus (Fig. 1).

Passive membrane properties of hippocampal neurons

The comparative electrophysiological characteristics of these neurons are summarized in Table 1. Cells in control group (n=6) typically fired in a tonic discharge mode with an average firing frequency of 2.4±0.9 Hz. The input resistance was determined by injecting a series of hyperpolarizing constant current pulses of increasing amplitude into the neurons and measuring the membrane potential deflections produced. The input resistance then was calculated from the slope of the resultant regression line, which yielded an average value of 39.4±6.1 MΩ. The time constant of the membrane was determined by calculating the time required for the membrane potential

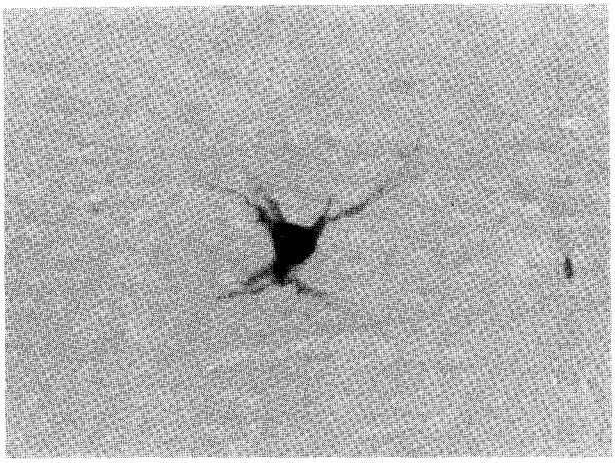

Fig. 1. Photomontage of a pyramidal neuron recorded in vivo and stained intracellularly with neurobiotin.

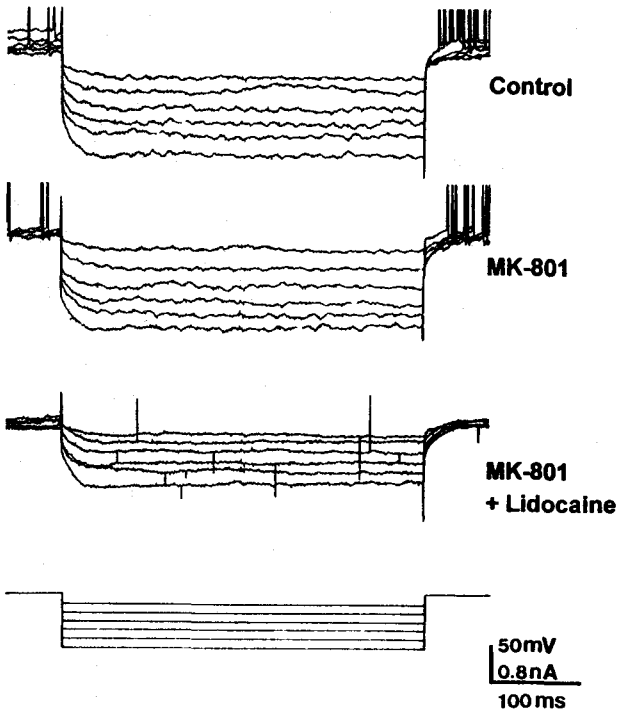

Fig. 2. Response of a pyramidal cell to hyperpolarizing current steps. Input resistance was determined by injecting a series of hyperpolarizing constant current pulses of increasing amplitude and 400 ms duration (bottom) and measuring the membrane potential deflections produced (top).

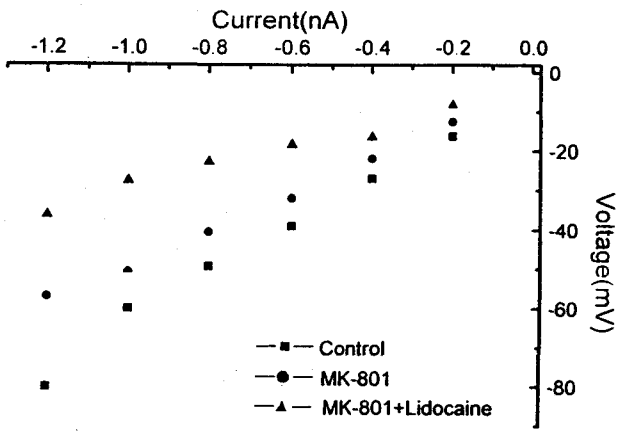

Fig. 3. Current-voltage curve of the neuronal cells. Input resistance was calculated from the slope of regression line obtained by plotting data.

to reach 1/(1-e) (i.e., 63%) of the peak membrane hyperpolarization produced in response to injection of low amplitude, hyperpolarizing constant current pulses (−1.0 nA, 400 ms). The time constant in these

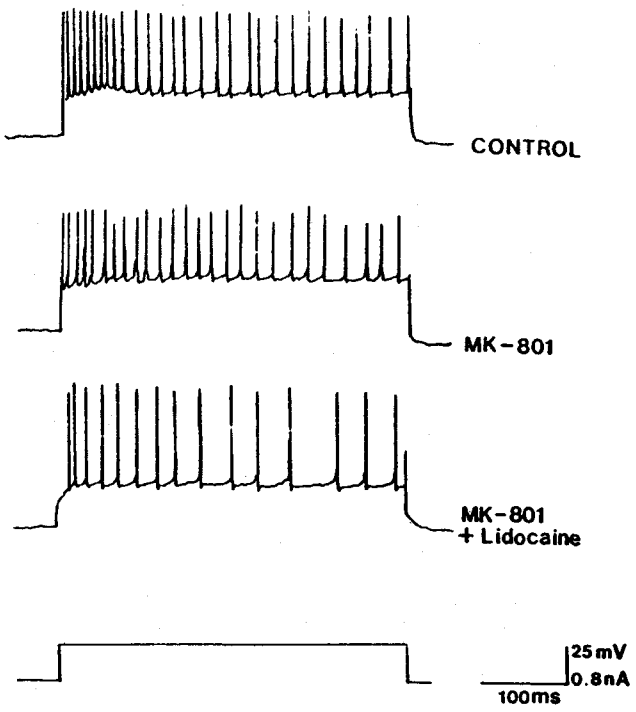

Fig. 4. Response of a pyramidal cell to depolarizing current. Injection of depolarizing current pulses (+0.8 nA) evoked trains of action potentials in pyramidal cells. Neurons in control group showed a slowing of spike firing during a depolarizing pulse.

cells was calculated to be 7.7±1.7 ms (Fig. 2). Furthermore, cells tested exhibited accommodation of spike firing when the membrane was depolarized for periods of 400 ms (Fig. 4).

Neuron in MK-801 treated group (0.2 mg/kg, i.p., n=4) had an average input resistance of 32.8±5.7 MΩ and a membrane time constant of 7.4±1.8 ms. These neurons exhibited 2.4±0.2 ms spike durations, which were similar to the average spike duration recorded in neurons of the control group. Slightly less than half of the these neurons were firing spontaneously at an average discharge rate of 2.4±1.1 Hz. The average peak amplitude of the AHP following the spikes in these group was 7.4±0.6 mV with respect to the resting membrane potential (Fig. 3).

Cells in MK-801 and lidocaine (5 mg/kg, i.c.v.) treated group (n=4) had an average input resistance of 34.5±6.0 MΩ and an average time constant of 8.0±1.4 ms. The cells were firing spontaneously at an average discharge rate of 0.6±0.4 Hz. Upon depolarization of the membrane by +0.8 nA for 400 ms, all of the tested cells exhibited accommodation

of spike discharge (Fig. 5).

Stimulus-evoked responses of hippocampal neurons

One of the major inputs of the hippocampal system is the commissural pathway. An examination was made to determine whether any of pyramidal cells treated with MK-801 and/or lidocaine could be activated upon fimbria-fornix stimulation. Stimulation of the commissural pathway evoked two different responses in pyramidal cells: excitatory postsynaptic potentials (EPSPs) and inhibitory postsynaptic potentials (IPSPs).

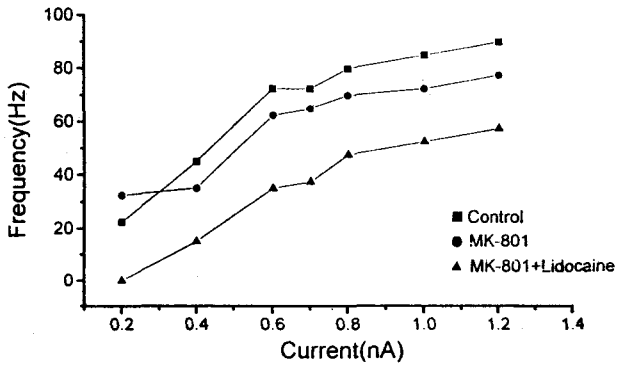

Fig. 5. Graph of frequency of firing as function of injected current during the depolarizing pulse. Pyramidal cell responses to depolarizing current pulses of increasing intensity. Note the progressive lengthening of the interspike interval during these responses.

Cells in control group were tested for their response to single pulse stimulation of the commissural pathway. These cells exhibited evoked EPSPs and IPSPs. Neurons in MK-801 treated group responded with evoked EPSPs and IPSPs upon the commissural pathway stimulation. In the group of cells with MK-801 and lidocaine, all of the neurons tested exhibited identical responses to that of the MK-801 treated cells to external stimulation (Fig. 6).

The more typical synaptic response to stimulation of the fimbria region consisted of an early-IPSP and a long-lasting late IPSP preceded by an EPSP. The late-IPSP reversal was extrapolated at -81, -98, -108 mV (control, MK-801, MK-801+lidocaine group), indicating the involvement of K ions and most likely postsynaptic $GABA_B$ receptors. An early-IPSP reversal was -68, -72, -63 mV (control, MK-801, MK-801+lidocaine group), indicating the involvement of Cl ions and probable postsynaptic $GABA_A$ receptors (Fig. 7).

EPSPs amplitude was affected by hyperpolarization applied through the recording pipette, as demonstrated by significant regression coefficients (e.g., $r = -0.98$, $P<0.0001$) of plots of EPSP amplitudes versus membrane potential. This result suggests that EPSPs are not generated postsynaptically at sites distal to the soma, but are more likely on proximal dendrites. No singnificant modifications of EPSP, early-IPSP, or late-IPSP components were detected in a MK-801 and/or lidocaine treated group.

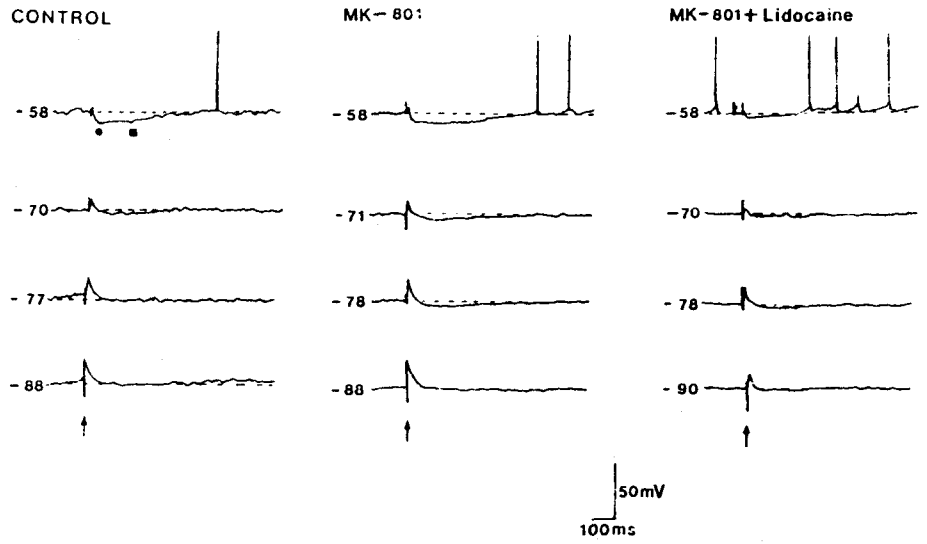

Fig. 6. Intracellular responses of pyramidal neuron to stimulation of the commissural path in vivo. Both an early IPSP (●) and late IPSP (■) were evoked by single pulses (arrow).

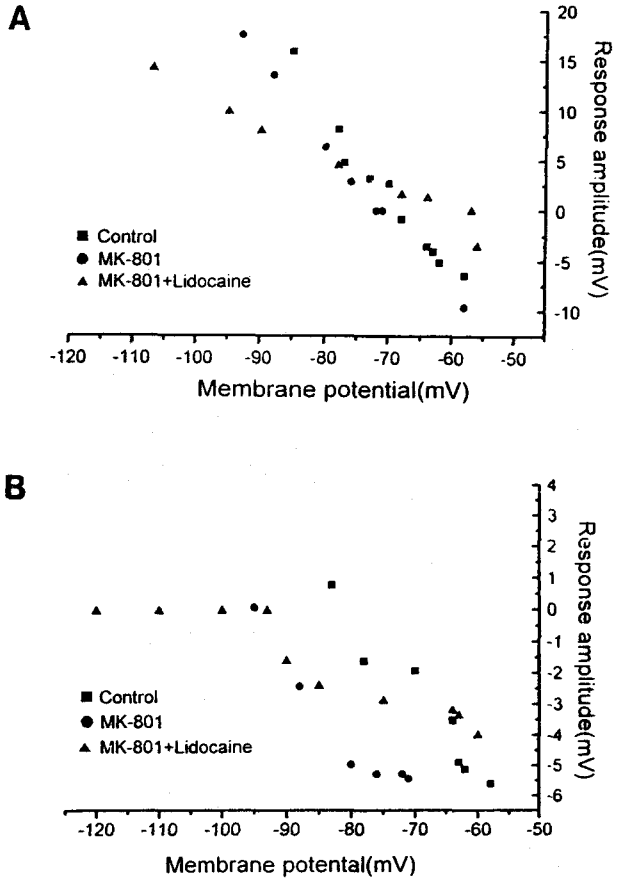

Fig. 7. Current versus voltage plot of the evoked response amplitude. Plot of amplitude versus membrane potential of early IPSP (A) and late IPSP (B).

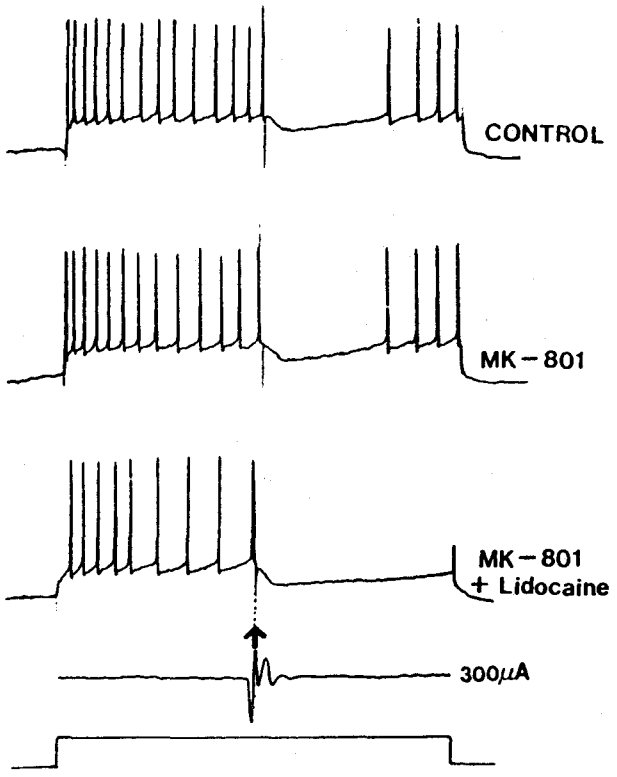

Fig. 8. Simultaneously evoked responses by commissural pathway and intracellular current injection. Evoked field response by an extracullular electrode in the pyramidal layer (bottom) and an intracellular response (above three traces).

Stimultaneously evoked responses by commissural pathway and intracelluar current injection were recorded to evaluate the relation between nerural network and pyramidal cells (Fig. 8).

DISCUSSION

Many of the basic membrane properties and evoked responses of hippocampal neurons recorded in vivo were similar to those observed in vitro (Sylviain et al, 1994), except that the neurons recorded in the intact preparation were under the continuous influences of spontaneous synaptic potentials. Thus, unlike the brain slice preparation, the activity of the neurons recorded in vivo is driven by their afferent input. This input appears to subserve several functions that differentiate basal activity in the intact preparation: such as driving spontaneous spike firing, determining the state of the bistable membrane potential, augmenting the impact of low threshold spikes, and subserving a primary role in the generation of rhythmic oscillations. To investigate the degree of convergence and interaction among afferents arising from widely dispersed brain nuclei onto single hippocampal neurons and in particular, to facilitate the assessment of the functional impact of these afferents on hippocampal cell activity state, it was necessary to use the in vivo preparation (O'Donnel & Grace, 1995).

Most of the basic physiological properties of hippocampal neurons recorded in vivo were analogous to those reported using in vitro preparations. The membrane potential of these cells was within the range of those reported in vitro. Cells recorded in MK-801 and lidocaine preparations exhibited a slow depolarization preceding spike discharge that corresponds to the decrease in the slope of the I-V plot at hyperpolarized membrane potentials. Direct polarization of cell membranes which were treated with

Table 1. Changes in membrane properties of hippocampal CA1 pyramidal neurons

Characterstics	Control	MK-801	MK-801+Lidocaine
Resting membrane potentials(mV)	−64.5±2.8	−67.1±4.2	−70.6±5.0
Spontaneous activity(Hz)	2.4±0.9	2.4±1.1	0.6±0.4
Time constant(msec)	7.7±1.7	7.4±1.8	8.0±1.4
Input resistance(MΩ)	39.4±6.1	32.8±5.7	34.5±6.0
Burst AHP amplitude(mV)	7.3±0.8	6.0±1.0	5.80±1.15
Spike Duration(msec)	2.4±0.3	2.4±0.2	2.5±0.2

All values are mean±S.E.

MK-801 and lidocaine manifested frequency and amplitude of the membrane potential changes, assuming that changing the membrane potential activates or inactivates most of the ionic conductances. The results of this study suggest that the effect of MK-801 and lidocaine in vivo is determined not only by intrinsic membrane properties but also is driven by afferent processes (O'Donnel & Grace, 1995).

The data obtained from this study leads to a conclusion that the lidocaine and MK-801 modulate the hippocampal neuron activity (Table 1). The most prominent and consistent effects of lidocaine and MK-801 are a blockade of burst AHP and an increase in the synaptic barrage. Lidocaine and MK-801 exerts only a small effect on the membrane potential: slight depolarization and slight hyperpolarization. The effects of lidocaine and MK-801 are fairly uniform and in many respects comparable to those reported for hilar neurons (Bijak & Misgeld, 1995). The blockade of the slow AHP dramatically alters the firing properties of pyramidal cells by removing spike frequency accommodation (Haas & Konnerth, 1983). In the majority of pyramidal neurons to which we treated lidocaine and MK-801, such an obvious effect on discharge properties was not seen. The adaptation was not altered by lidocaine and MK-801, suggesting that a conductance may underlie this adaptation similar to the calcium activated K conductance (Sah et al, 1985). In the presence of lidocaine and MK-801, the discharge rate of spontaneously active neurons decreased. A speculation can be drawn that the decrease in the spontaneous discharge rate may have resulted from lidocaine and MK-801- induced barrage of IPSP; however, no change in discharge rate was also observed after the blockade of glutamatergic transmission by MK-801.

Spike activity in hippocampal neurons could be evoked at varying degrees by stimulating each of the three primary excitory afferents to this region: the association path (Schaffer collateral system), commissural afferents, and direct entorhinal input (Attila et al, 1995). In this study, every hippocampal neuron tested exhibited some level of synaptic activation in response to stimulation of commissural pathway. Stimulation of fimbria-fornix resulted in an EPSP followed by IPSPs, probably due to activation of GABAergic collaterals. Although EPSPs were evoked in hippocampal cells from each stimulation site in most of cases, these stimuli typically were not capable of evoking discharge, suggesting that the activation of several convergent inputs may be required to trigger spike firing in these cells. Therefore, the high degree of convergence of excitatory inputs may be necessary for the transfer of information through the hippocampus.

Given the comparatively low degree of variability in the rate-of-rise and amplitude of the evoked responses observed in each cell upon stimulation of these pathways, the responses are more likely to occur due to a direct synaptic input to each cell. The constant latency of the responses evoked stimulation of commissural pathway is typically taken as evidence of a monosynaptic response. This study found that synaptic responses observed following the single stimulation of the commissural pathway include rapid depolarizations, rapid Cl^--dependent hyperpolarization, and long-lasting K^+-dependent hyperpolarization. The fact that EPSPs were significantly affected by modifications of the membrane potential agreed with excitatory inputs on close elements of the recorded pyramidal neurons of the hippocampus (Branchereau et al, 1996). The excitatory and inhibitory synaptic events arising from single electrical stimulation of the commissural pathway may also be

involved in responses induced by lidocaine and MK-801. However systemic injection of the NMDA antagonist MK-801 and lidocaine did not affect the complex responses to single electrical stimulation of the commissural pathway, suggesting that glutmatergic fibers are not directly implicated in the responses.

The complex synaptic responses composed of EPSP, Cl^--mediated early-IPSP, and K^+-mediated late-IPSP after the stimulation of the commissural pathway are typical responses of rat neocortical neurons to afferent stimulation (Connors et al, 1988; Cox et al, 1992; Kawaguchi, 1992)

The electrophysiological results of this study indicate that the observed inhibitory component of the complex synaptic response to the stimulation of commissural region involve mainly $GABA_B$, but not $GABA_A$ receptors (Branchereau et al, 1996). Although the enhancing effect of lidocaine and MK-801 on the spontaneous IPSPs is not proved, this study demonstrates strong modifications in early and late IPSP after the injection of MK-801 and lidocaine in response to electrical stimulation of the commissural pathway. The cause of these modifications was the orthodromic activation of hippocampal GABAergic neurons, which innervate the pyramidal cells (Branchereau et al, 1996).

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