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EFFECTS OF LIDOCAINE ON SOMATOSENSORY EVOKED POTENTIALS IN RAT VIBRISSA/BARREL CORTEX

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Abstract

리도카인이 흰쥐 피질의 체성감각 유발전위에 미치는 영향

최병주 · 이혜숙 · 김영진** · 남순현** · 김현정** · 이만기*

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본 실험은 삼차신경 자극으로 발생되는 체성 감각 유발 전위에 대한 국소마취제의 효과를 관찰하였다. 나트륨 통로차단을 통하여 약리작용을 나타내는 것으로 알려져 있는 리도카인를 뇌 피질에 국소 투여한 후 삼차신경의 체성 감각유발 전위의 강도및 지연시간을 측정하였다. 케타민으로 마취된 흰쥐의 대측성 구레나룻 자극후 뇌의 체성 감각영역으로부터 기록되는 유발전위를 분석한 결과, 리도카인을 뇌 피질에 국소 투여시 유발전위의 강도 및 지연시간의 감소가 나타났으며, 필드 전위의 형태는 이상성(양극성 및 음극성) 혹은 삼상성(양극성, 음극성 및 양극성)의 파형으로 나타났다. 필드 전위의 발생 부위는 뇌 피질의 중대뇌동맥의 상행지 상방영역이었다. 본 실험에서 나타난 초기 전위변동은 피질판 상층에 존재하는 신경세포의 탈분극 과정에 의하여 생성되고 후기의 전위 변동은 동일 영역의 하층 신경세포에서 과분극 혹은 재분극이 발생한 결과라고 유추된다. 따라서 삼차신경계의 체성 감각 영역에서는 피질 상층및 하층의 과립성 피라미드 세포의 순차적인 활성화에 의하여 기본적인 신경 회로망이 형성되어 있으며 생리적 자극으로 유발되는 필드 전위는 이러한 신경망를 통하여 발생될 것으로 사료된다.

I. Introduction

For the primary somatosensory cortex in various species of mammals, there is a precise somatosensory map of the body and face, including oral structures such as the tooth.[23] It is well known that primary somatosensory cortex is characterized by an organization of layer IV cells into distinct cytoarchitectonic units. These units were termed 'barrels' because of their shape in Nissl preparations. Barrels are arranged in direct topographical relation to the vibrissa on the animals snout, each barrel being structurally and functionally associated with a corresponding contralateral vibrissa. A major part of the barrel field consists of five prominent rows of five to seven large barrels. It was suggested that the potentials evoked by vibrissa stimulation were due to laminar interaction between two distinct populations of pyramidal neurons, one in the supragranular layers and another in the infragranular layers. The reports by Amstrong-James et al[2] suggest that stimulation of a single vibrissa results not only in activation of associated layer IV barrel, but also in local activation of cells in the supragranular and infragranular layers of the same cortical region. These results indicate that neurons in vibrissa/barrel cortex are functionally organized into vertical columns of which the barrels in layer IV are morphologically recognizable correlates.[58]

It is also indicated that the laminar arrangement of cells within each column reflect yet another functional and cytoarchitectural order, although rat vibrissal cortex is topographically arranged in discrete barrel-related columns. A number of studies[1,11,27,48] have provided evidence that the smallest receptive fields are found in the middle granular layers (IV and deep III) in vibrissa/barrel cortex. Receptive fields in cells of the supragranular layers are twice as large as the granular cells, and even larger in infragranular layers. Furthermore, study of response latency[10] has also demonstrated shorter latencies in layer IV, with longer delays in layers II-III and V. These data suggest that information may be processed within each barrel-related column in a spatially and temporally organized sequence along the laminar axis. Based on evidence from single-unit recordings, Simons[48] has proposed that processing within columns originates in layer IV and lower-layer III, proceeds to the superficial cortical lamina and finally to the deep lamina. Similar lamina-dependent processing has been extensively documented in somatosensory cortex of monkey[45], cat[36] and rat[33], and visual cortex of monkey[26] and cat[25].

The sequential laminar interactions measured in single-unit studies of rat vibrissa/barrel cortex are similar to those derived from extracellularly recorded postsynaptic field potentials during evoked responses to epicortical electrical stimulation and during evoked and spontaneous epileptic spikes of the penicillin focus[6,7,16,17,18,41,42,43,44].

In this study, the effect of topical application of lidocaine, a sodium channel blocker, into the cortex on the amplitude and latency of cortical somatosensory evoked potentials were measured. The objective of the present experiment was to extend our method of field potential analysis to the study of evoked responses in vibrissa/barrel cortex and to compare patterns of electrical activities produced by normal physiological stimulation with those by lidocaine stimulation.

II. Material and Method

1. Animal surgery

Adult Sprague-Dawley rats (300-350g) were used and anesthesia was done with a

combination of ketamine HCl(60mg/kg) and xylazine (13mg/kg). A unilateral craniotomy was performed to expose a parietotemporal cortex. The dura was removed and the exposed cortex was covered with saline throughout the experiment.

2. Stimulation of vibrissa

Large mystacial vibrissa (mostly C2) were selected for stimulation because of their well-known large corresponding barrel representation in the cortex. The vibrissa were cut to a length of 12 mm and attached to the tip of a orthodontic wire. The probe was driven by a laboratory-built stimulator that used a small audio speaker into vertical mechanical movements up to several millimeters. In the present study, brief (50 ms) monophasic pulses were used to produce vibrissa displacements of ~0.5mm excursion in the dorsoventral direction. This stimulation setting produced highly repeatable evoked cortical responses in preliminary experiments.

3. Field potential recording

The evoked potentials were recorded from a Ag electrode. The electrode was advanced by 50μm and inserted perpendicular to the cortical surface. Evoked potential session was carried out before and immediately after drug administration. Electrical signals were preamplified with AI 405 probe (Axon Co.) and transferred to Cyberamp 380 (Axon Co.). The connector of the recording cable was plugged into the AD converter and electrophysiological data acquisition was started. The raw evoked potentials were continuously displayed on the screen of the computer. The electrophysiological data were stored on a hard disk. With the use of ascending branches of the middl e cerebral artery as an approximate landmark [5,51], the projection region of a given vibrissa in the somatosensory cortex was localized in the optimal responses (shortest latency and highest amplitude potential) recorded from a surface electrode. Evoked field potentials were digitally sampled (400 Hz ; 2.5 ms) and both single trial data and averaged responses (n=20) stored on disk for further analysis.

III. Results

Lidocaine was injected through a 50μm micro syringe (Hamilton CO. Reno. Nev.) fixed in a animal holding apparatus into the ipsilateral area (Fig. 1). Topical application of lidocaine was made by advancing the plunger manually. Field potentials were recorded every 2 or 10 min with silver electrode. Fig.2 shows an test paradigm used to evaluated evoked potentials. EEG activity and response to sound was recorded to rule out the possibility of the engagement of sound stimuli to the evoked potentials. After confirming these things, physiological saline and adequate lidocaine were applied to the brain surface. Averaged evoked potentials elicited at surface in SI area by vibrissa stimulation had one large positive and one negative component or triphasic (positive-negative-positive) (Fig.3). These components were reduced within 2 min after a lidocaine application into somatosensory area (SmI). The amplitude of the positive component showed the largest change in amplitude among these components. Following the high dose (10 mg/kg) of lidocaine application, a component of the somatosensory evoked potential was partially abolished at 5 min and the evoked potential returned to just below the control level within 15 min (Fig. 4A). Application of low dose (0.5 mg/kg) of lidocaine had no effect on somatosensory evoked potential (Fig. 4B). The inhibitory effect of lidocaine (11.1 mg/kg) on field potentials reached a

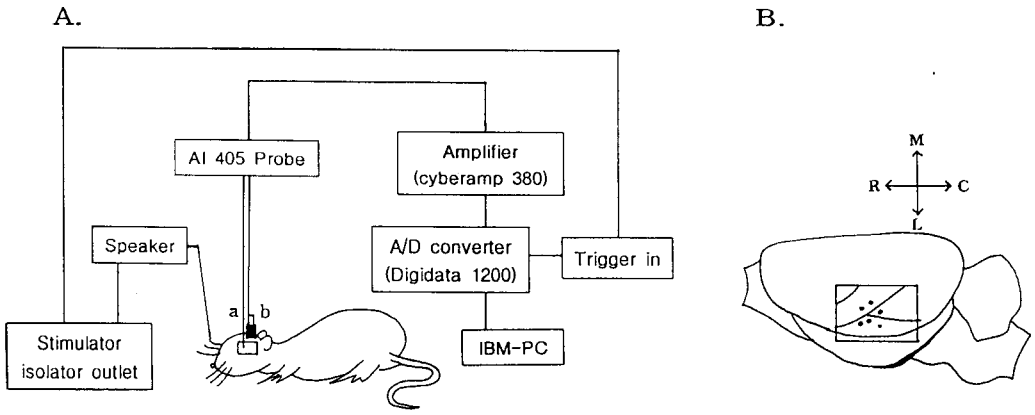

Fig. 1. Schematic diagram of experimental apparatus used in this study (A) and recording points on the surface of the rat cerebral cortex(B). Black points in window of (B) indicate recording sites. a, recording electrode; b, reference electrode.

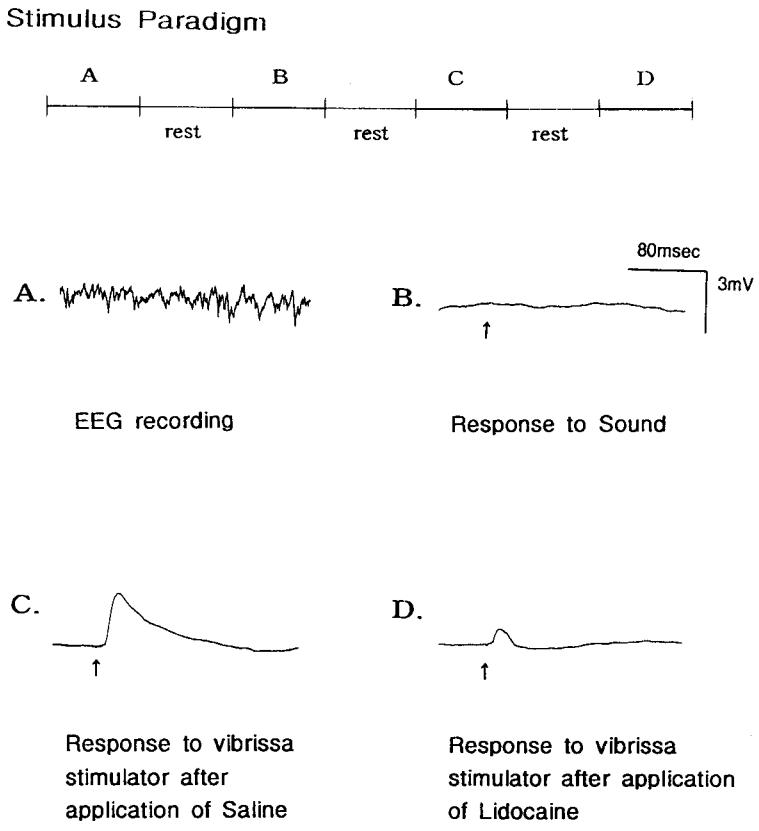

Fig. 2. Protocols and test paradigm used to evaluate evoked potentials. The stimulus paradigm (top) indicates the sequence of events for both sound and vibrissa stimulation. An arrow indicates onset of stimulation.

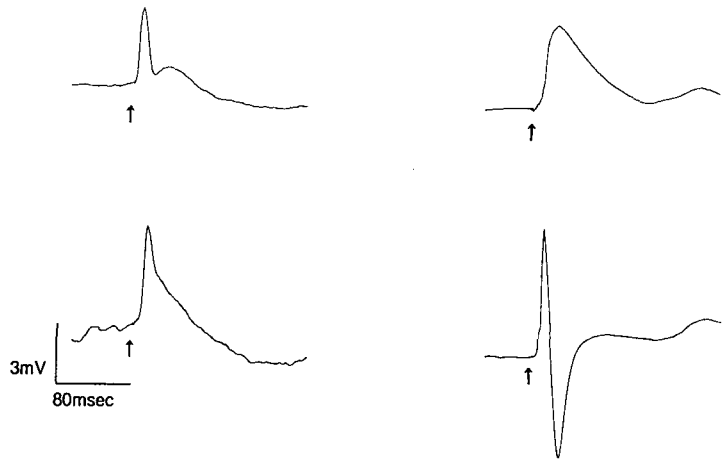

Fig. 3. Representative figures of evoked potentials induced by stimulation of vibrissa. An arrow indicates onset of stimulation.

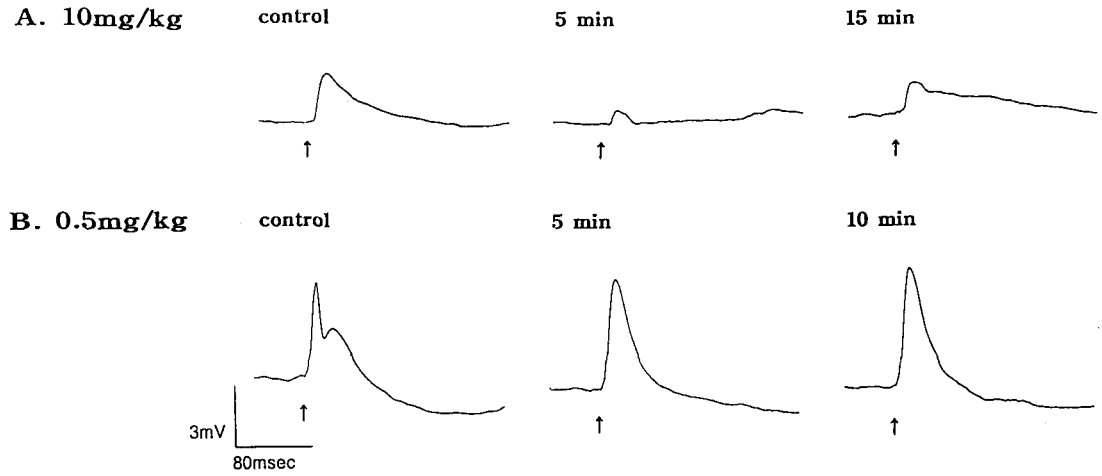

Fig. 4. Effects of lidocaine injection into somatosensory cortex on field potentials elicited by vibrissa stimulation. The field potentials, representing an average of 20 stimulus trials, were recorded before control, at 5 min, and 15 min after lidocaine injection into cortex. Note that field potentials have recovered by 15 min after injection. An arrow indicates onset of stimulation.

maximum about 2-5 min after completion of the injection and had disappeared by 20-30 min (Fig. 5). The time course was similar to that reported by Burton and Robinson. In all experiments, SmI field potentials were collected in the temporal area of the gyrus which receives projections from vibrissa.

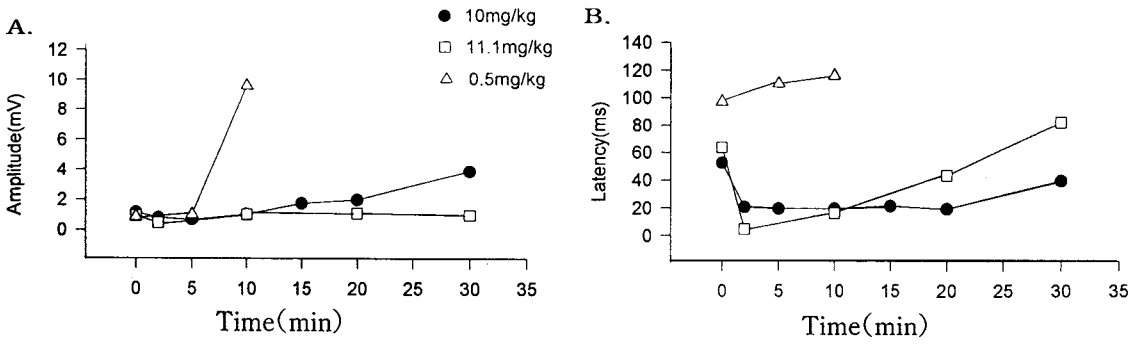

Fig. 5. Time course of the effect of application of lidocaine into the cortex on the amplitude (A) and latency (B) of cortical somatosensory evoked potentials

Ⅳ. Discussion

The sequence of electrophysiological events in the vibrissa barrel cortex evoked by vibrissa stimulation was due to laminar interaction between two dictinct populations of pyramidal neurons, one in the supragranular layers and another in the infragranular layers. The supra- and infragranular cell populations are a small pyramidal cell with short apical dendrites in layers Ⅰ-Ⅲ, and a larger pyramidal cell with its soma in layers Ⅴ-Ⅵ and longer apical dendrites extending to the cortical surface, respectively.

It can be proposed that there are methodological limitation in our paper. In general, anesthetics render the somatosensory receptive field smaller and the responses are stable than in the awake preparation. The present data with anesthetized animals therefore do not reflect cortical function fully. The extracellular field potentials were recorded by electrodes with relatively large contacting areas compared with electrodes used in single unit activities. The resulting potentials therefore reflect the sum of potentials in that region, including neurons differing in location and laminar extent. These summed potentials are probably dominated by the activity of pyramidal neurons because of their size, number, concentration and morphometry. But these limitations of our methodology made it simple to conclude the results in the present paper.

There are many papers about morphological and anatomical connection in cortical pyramidal cells. White[56] has reported that at layers Ⅳ-Ⅴ border in mouse SmI cortex, there are bipolar cells that receive direct input from thalamocortical fibers. These bipolar cells have two thick primary dendrites, on directed toward cortical surface and the other toward the white matter, parallel with the processes of cortical pyramidal neurons. Peters and Kimerer[40] have suggested that the primary role of these cells in the cerebral cortex is to excite clusters of pyramidal cells. With major dendrites projection above and below the cell body, synaptic activation on dendrites proximal to the soma of bipolar cells would be expected to result in symmetrical return currents. Therefore, the evoked potentials activated by physiological stimulation may reflect activity of a separate subpopulation of bipolar cells in deeper layers that covaried over time with the supragranular cells. But the results in the present paper can not distinguish between these possibility. We can assume that there are different mechanism and varying cellular

activation according to time course of the evoked potentials. Our data about normal curve of evoked potentials show initial positive response and late negative response. Intracellular recordings demonstrate that vibrissa displacements evoke initial excitatory postsynaptic potentials (EPSPs)[1,19,24] with shorter latency in layer IV[10]. It has also been reported in various species that evoked responses in the somatosensory as well as visual and auditory cortex are initiated by excitatory processes[50,54] that are thought to be mediated by fast-conducting thalamocortical afferents, eliciting postsynaptic excitatory responses directly or indirectly at the deeper parts of small pyramidal neurons in the upper cortical lamina[31,32,35]. Extracellular studies in other species provide further indirect evidence that neuron discharges in the SmI cortex evoked by cutaneous stimulation last as long as 30 ms[21,31] and reflect a predominant excitation during this period. There may be two possible pathways mediating the depolarization of the infragranular pyramidal neurons. Similar to the supragranular neurons, thalamocortical afferents make extensive excitatory monosynaptic connections with apical dendrites of infragranular cells[28,55,56,57], producing short-latency activation.

A number of studies in rat as well as cat have shown that vibrissa stimulation evokes from SmI cortical neurons longer latency IPSPs of 30- to 200-ms duration after short initial EPSPs, and a cessation of spike discharges extends through this period[10,19,24], indication inhibitory nature of these events. Conners et at[13] reported that the pyramidal cells in the rat SmI cortex generate a long-lasting IPSP, which follows the short-latency IPSP, beginning at -50-ms poststimulus. This long lasting IPSP could be evoked from dendritic sites of pyramidal cells. In studies of excitatory inhibitory response sequences in SmI cortex, Steriade[50] identified a long-lasting period of hyperpolarization of 100- to 200-ms latency. On the basis of intracellular recording, it was concluded that this late inhibitory process is due to a Ca^{2+}-dependent increase in K^+ conductance. The present data that topical application of lidocaine decreased the amplitude but not changed morphology of potentials support a basic model of sequential information-processing in laminar neocortical circuitry that has been proposed by several authors[25,26,31,35,36]. During the vibrissa-evoked response, specific thalamocortical fibers directly input to cortical layer Ⅳ and lower-layer Ⅲ, producing short-latency postsynaptic excitation of the proximal dendritic regions of short pyramidal cells monosynaptically and bisynaptically via interneurons. The primary site of depolarization quickly shifts to distal apical dendrites of the infragranular cells, possibly through direct thalamocortical connections as well as through excitatory spiny stellate cells and collateral fibers from the supragranular pyramids. This excitatory sequency is followed by hyperpolarization and repolarization processes, first at the distal apical dendrites of the supragranular cells and then at similar locations on the apical dendrites of infragranular cells. This simple laminar circuit must therefore reflect fundamental cytoarchitectural features of columnar neocortex. Another analysis method may be needed to study spatially and temporally overlapping interactions between supragranular and infragranular cells during physiological activation of vibrissa/barrel cortex, providing complementary information to that obtained from unit recording.

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