EFFECTS OF PENTYLENETETRAZOL, PENTOBARBITAL AND LIDOCAINE ON PALLIDAL UNIT ACTIVITIES IN RATS

Junko MORI and Takeo FUKUDA*

*Department of Physiology, National Defense Medical College,
Tokorozawa, Saitama 359, Japan*

** Department of Pharmacology, Faculty of Medicine,
Kagoshima University, Kagoshima 890, Japan*

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Abstract—In anesthetized immobilized rats, pallidal unit activities were recorded extracellularly through glass microelectrodes. Spontaneous activities were converted to an interspike interval histogram and an autocorrelogram by a medical computer and a correlator. Following pentylenetetrazol injection (20 mg/kg i.v.), burst discharges increased remarkably and the bursts tended to synchronize with repetitive spikes in electrocorticogram. Following administration of liocaine (5 mg/kg i.v.) the bursts increased by pentylenetetrazol were facilitated in approximately 70% neurons, whereas pentobarbital showed obvious reduction of the bursts in 80% neurons, although both drugs reduced the firing rate. Facilitation of burst discharges was also observed with high doses of lidocaine alone. These results indicate that lidocaine, as compared with pentobarbital, may block more easily inhibitory rather than excitatory neurons.

Systemically administered local anesthetic agents such as procaine and lidocaine suppress the tonic extension of maximal electroshock convulsions in experimental animals (1), whereas the drugs tend to enhance the clonic phase of convulsions (2). Furthermore, a single administration of these drugs in higher doses induces clonic convulsions (2). On the other hand, barbiturates such as phenobarbital suppress both clonic and tonic phases of the convulsions induced by pentylenetetrazol or electroshock. Such a difference between the effect of local anesthetics and that of barbiturates on the manifestation of convulsions may be due to different mechanisms of their depressant actions on the central nervous system. We previously reported that lidocaine blocked inhibitory neurons in the reticular formation of rats more easily than did pentobarbital (3), and Galindo (4) also showed similar effects of procaine and pentobarbital on cuneate neurons of cats.

Globus pallidus is regarded as one nucleus which plays an important role in occurrence of clonic convulsions (5). We have already reported that more than half the number of pallidal neurons showed sporadic burst discharges in their spontaneous firings and that the burst discharges were enhanced by pentylenetetrazol injection (6). In the present work, we investigated the effect of high doses of lidocaine on pallidal unit activities and also influences of lidocaine and pentobarbital on the bursts increased by pentylenetetrazol.

MATERIALS AND METHODS

Male and female adult Wistar rats weighing 200–350 g were used. Surgical procedures

were performed under ether anesthesia. The trachea was exposed to insert the cannula, the animal was immobilized with decamethonium bromide (20 mg/kg i.v.), and then artificially respiration through a tracheal cannula. After fixation on a stereotaxic instrument, the skull was exposed and the following electrodes were inserted stereotaxically.

A glass microelectrode filled with 2M potassium citrate was inserted into the globus pallidus at the coordinates, A: 6.0–6.5, L: 2.0–2.5, D: -1.5–0.5 according to the brain map of König and Klippel (7) to pick up single unit activities. Drugs were injected through a catheter into the femoral vein. Electroencephalogram from sensorimotor cortex and electrocardiogram were simultaneously monitored by an oscilloscope for observation of the animal condition during the experiment. The location of microelectrode was checked histologically after the experiment.

Spontaneous activities from pallidal neurons were recorded and stored on a magnetic tape recorder (R-100, TEAC) and were converted to an interspike interval histogram by a medical computer (Signal Processor, Sanei Co.) and to an autocorrelogram by a correlator (C-100, TEAC). The interspike interval histogram was formed from discharges for 1–3 min with 0.16 msec sampling time, and in such cases interspike intervals longer than the maximal interval (64 msec) were excluded. The sampling time in the autocorrelogram was 0.4 msec and the duration of analysis 1–3 min.

RESULTS

A total of 72 units in globus pallidus were recorded. Fig. 1 shows the effect of i.v. administration of pentyleneetetrazol (20 mg/kg) on the activities of a pallidal neuron. A few spontaneous burst discharges were seen among sporadic background activities before injection (Fig. 1A). Pentyleneetetrazol increased the burst discharges and background single spikes (Fig. 1B), and finally induced repetitive rhythmical bursts synchronized with spikes on the electrocorticogram (Fig. 1C).

Interspike interval histograms and autocorrelograms of pallidal unit activities after pentyleneetetrazol are shown in Fig. 2. Though no marked peak interval was observed in the control, the increase of burst discharges was clearly reflected on the histogram after pentyleneetetrazol injection and particularly discharges within 3–4 msec spike intervals increased markedly. In autocorrelograms, two high peaks appeared at 3–4 msec and 7–8

FIG. 1. Effect of intravenous injection of pentyleneetetrazol (20 mg/kg) on pallidal unit activities. A: Before injection. B: Immediately after injection. C: 5 min after injection. Electrocorticogram recorded simultaneously is shown at the upper beam in C. Note the bursts synchronized with spikes in corticogram.

FIG. 2. Interspike interval histograms (left) and autocorrelograms (right) of pallidal spontaneous unit discharges. In interval histograms, the number of unit discharges at every 0.16 msec interval is plotted on the ordinate and the firing rate per sec is shown at each graph (10.2 and 11.7). In autocorrelograms the possibility of appearance of discharge within 0.4 msec is represented on the ordinate. 51-1 represents reference number of the neuron, of which a part of the original pattern is shown in Fig. 1.

FIG. 3. Effects of pentylenetetrazol (PTZ) and successive administrations of pentobarbital (PB) on pallidal neuronal activities. Left column: Interval histograms. Right column: Autocorrelograms. Note that the increase of discharges at 2-3 msec intervals and of firing rate after PTZ was suppressed by administration of PB.

msec intervals following pentylenetetrazol. Such a pattern indicated that the spikes within the bursts induced by pentylenetetrazol were composed of 3–4 msec intervals. Autocorrelograms in other samples also showed the first peak at 2–4 msec intervals.

The bursts which increased remarkably after pentylenetetrazol injection were depressed by successive injections of pentobarbital (5 mg/kg) (Fig. 3, left) and the total firing rate was diminished. The result was shown more clearly in the autocorrelogram of which pattern changed from peaky to rather flat (Fig. 3, right). The effect of lidocaine on the total firing rate and the bursts after pentylenetetrazol was quite different from that of pentobarbital. As shown in Fig. 4, lidocaine (5 mg/kg) facilitated the bursts, whereas it reduced the total firing rate. The 3–4 msec intervals which reflected the firings within the burst were increased further and the longer intervals of background firings were reduced after lidocaine. The effects of both drugs disappeared within 30–60 min though the effect of lidocaine tended to disappear earlier than that of pentobarbital.

The data obtained from 27 pallidal neurons of lidocaine administration and 18 of pentobarbital in pentylenetetrazol treated rats are summarized in Fig. 5. Both drugs

FIG. 4. Effects of pentylenetetrazol (PTZ) and successive administration of lidocaine (LID) on pallidal neuronal activities. Note that the appearance of discharges at 3–4 msec intervals after PTZ administration was facilitated by LID despite a decrease in firing rate. Compare these effects with those after pentobarbital in Fig. 3.

FIG. 5. Effects of lidocaine and pentobarbital on the discharges changed by pentylenetetrazol in pallidal neurons. Unfilled bars represent the action of lidocaine following pentylenetetrazol (PTZ-LID) in 27 neurons and filled bars represent the action of pentobarbital following pentylenetetrazol (PTZ-PB) in 18 neurons. The drug effects are summarized in reference to firing rate and bursts. The number of neurons affected by drugs is shown as a percentage on the ordinate, and each change on the abscissa ($\uparrow$: increase, $\sim$: no change, $\downarrow$: decrease). Note the discrepancy between the effects of both drugs on the burst.

FIG. 6. Effects of lidocaine on pallidal neuronal activities. The discharges were composed of only bursts after lidocaine injection.

reduced the total firing rate in more than half the number of tested neurons. The effects of lidocaine and pentobarbital on the burst discharges increased by pentylenetetrazol were quite different. Lidocaine facilitated the bursts in approximately 70% of neurons, whereas pentobarbital inhibited the bursts in more than 80% of neurons.

Fig. 6 represents the effect of a single application of a high dose of lidocaine on the activity of a pallidal neuron. In this neuron, burst discharges did not appear before injection, but immediately after injection of lidocaine (20 mg/kg), the background discharges

FIG. 7. Effect of lidocaine on 27 pallidal neuronal activities (expressed in the same way as Fig. 5).

were reduced and spikes appeared as bursts only. The results from 27 neurons after lidocaine injection are summarized in Fig. 7. Though high doses of lidocaine reduced the firing rate in 60% of neurons, this drug increased the burst discharges in more than half the number of neurons.

DISCUSSION

We previously pointed out the difference between the effects of lidocaine and pentobarbital following pentylenetetrazol injection, on the activity of pallidal neurons by observing the interspike interval histogram with 10 msec sampling time (6). In the present paper, we observed interval histograms with a shorter sampling time (0.16 msec) to investigate burst discharge in the pallidal spontaneous activities. In addition, autocorrelograms which distinguish the bursts more clearly were employed. The experimental results strongly indicate that lidocaine facilitated the burst discharges increased by pretreatment of pentylenetetrazol, whereas pentobarbital suppressed these discharges. The difference between the effects of both drugs on the activity of pallidal neuron was thus reconfirmed.

Sawa (8) reported the appearance of burst discharges at occurrence of convulsion as a result of inhibition of inhibitory synaptic potential. The discrepancy between the effect of lidocaine and that of pentobarbital on the burst may be due to the difference of sensitivities of inhibitory neurons to both drugs. Tanaka and Yamasaki (9) reported that lidocaine did block inhibitory neurons more easily than excitatory ones, and data of other investigators (10, 11, 12) supported this suggestion. Moreover Miyahara et al. (13) described that the blocking action on inhibitory neurons is apt to appear with high doses of lidocaine given intravenously. The appearance of bursts after high doses of lidocaine in the present paper may be the result of such an effect.

On the other hand, Nakai et al. (14) reported that in the central visual pathway in cats, pentobarbital was more effective on facilitatory than on inhibitory modulation. The effect of pentobarbital on inhibitory neurons was seen as an enhancement of presynaptic inhibition by Miyahara et al. (13), and of postsynaptic inhibition by Hurlbrink and Boyd (15). Though

it is unclear whether facilitatory or inhibitory neurons are affected preferentially by pentobarbital, it is fairly certain that lidocaine has a more selective action upon inhibitory neurons than does pentobarbital.

Lidocaine had a contrary effect on the formation of burst discharges to pentobarbital and such may be related the fact that this drug enhances or induces clonic convulsion (2), whereas barbiturates inhibit the convulsion. The burst discharges following pentylene-tetrazol or high doses of lidocaine appeared in most cases without increase of sporadic spikes in the background. Ootsuji (5) reported the participation of pallidal neurons in the occurrence of clonic convulsions. Moreover, we confirmed the fact that the burst discharges of pallidal neuron following pentylenetetrazol were synchronized with spikes in electrocorticogram. In addition, the increase of burst discharges with administration of lidocaine was rarely seen in neurons in the reticular formation (3). Thus the increase of bursts in pallidal neuronal activities may play an important role in manifestation of clonic convulsions.

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