EFFECTS OF THE THALAMIC STIMULATION ON THE RETICULAR NEURON ACTIVITIES AND THEIR MODIFICATIONS BY LIDOCAINE AND PENTOBARBITAL

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It has been known that systemically administered local anesthetic agents such as procaine and lidocaine manifest depressant effects similar to barbiturates on the central nervous system. They abolished the tonic extensor phase of the maximal electroshock seizure in experimental animals (1-4), inhibited the reticular activating system (5), and blocked the amygdaloid (6) as well as hippocampal after-discharges (7).

On the other hand, some discrepancies were observed between the actions of local anesthetics and of barbiturates in behavioral and electrical manifestations of convulsion. Procaine and lidocaine in larger doses induced clonic convulsions. They did not modify or even enhanced the clonic phase of electrically induced seizure (8), whereas barbiturates could suppress it. Moreover, the local anesthetics tended to enhance the spike and wave complex in EEG elicited by bemegride in rabbits, whereas barbiturates definitely inhibited it (9). These inconsistencies may be due to different mechanisms of depressant actions of local anesthetics and barbiturates on neurons of central nervous system. In fact, Galindo (10, 11) showed different patterns of synaptic inhibition by procaine and pentobarbital in cuneate neurons of the oblongate medulla in cats.

We intend to search the difference in the mechanisms of inhibitory action of lidocaine and pentobarbital on the activities of reticular neurons, since the reticular formation is regarded as a site to play an important role in the manifestation of tonic convulsion (12, 13) and the activities of its neurons are closely related to cortical spikes induced by pentetrazol (14).

The present study is concerned with the midbrain reticular neurons of which activities are influenced by stimulation of the thalamic reticular nucleus.

METHODS

Male or female 72 adult rats of Wistar strain weighing 170-300 g were used in the experiment. Surgical procedures were performed under ether anesthesia. After tracheotomy and cannulation into the femoral vein, the animal was immobilized with decamethonium bromide (20 mg/kg). Under artificial respiration the animal was fixed in a stereotaxic instrument, and the experiment was carried out after ether anesthesia expired.

Single unit activities of midbrain reticular formation (MRF) were picked up with extracellular tungsten microelectrodes (1-2 μ on the tip) at the level of the red nucleus. Ipsi-
Fig. 1. Examples of two different single unit activities of MRF neurons.

A: This neuron increased firing frequency during 2 seconds of RT stimulation (0.1 msec, 100 c's, 8 V). The period of stimulation is distinguished by artifact.

B: This neuron stopped firing during RT stimulation (0.1 msec, 100 c's, 6 V).

Fig. 2. Histograms of single unit activity (spontaneous firing and responses to RT stimulation) of MRF neurons.

A: Fifteen sequence responses to RT stimulation were summed by a computer. Number of unit discharge in every 100 msec is plotted on the ordinate. Period of the stimulation is marked by underline. One response of this neuron is illustrated in Fig. 1A.

B: Summation of 40 sequence responses to RT stimulation by a computer. The photograph of one response of this neuron is shown in Fig. 1B.
lateral nucleus reticularis thalami (RT) was stimulated with a train of rectangular pulses for 2 seconds through the bipolar electrode made from enamel-coated stainless steel wire (100 μ in diameter). The parameters of stimuli were 0.1 msec, 100 c/s, 2–8 v. The sites of recording and stimulation were determined according to the brain map of König and Klippel (15).

As illustrated in Figs. 1 and 2, the activities of MRF single unit were converted to a histogram (spontaneous firing and responses to stimulation) by means of a medical computer (MEDIAC, Sanei Co.). The computer was operated by a trigger pulse of every 12 seconds. After 2 seconds of delay to the trigger pulse, the gate of stimulator was opened for 2 seconds, analysis time was 10 seconds in each sample and the summation of sequence of 15–40 samples was obtained.

Electrocorticogram (ECoG) from sensorimotor cortex and electrocardiogram (ECG)

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**FIG. 3.** Samples of three types of MRF neurons which responded to RT stimulation.

F-type: Facilitation of discharge rate during the stimulation.

I-type: Inhibition by the stimulation.

M-type: Mixed response of facilitation and inhibition during the stimulation.

In each histogram, the ordinate represents number of unit discharges in every 100 msec and the underline shows period of RT stimulation.
were simultaneously monitored by an oscilloscope for the observation of the conditions of animal during the experiment.

The position of the electrode in the thalamus and trace of microelectrode were verified histologically after the experiment.

RESULTS

1. Effects of thalamic stimulation on reticular neurons

In 72 rats, 576 single unit activities of MRF were recorded. They were classified into the following four types according to the discharge patterns during RT stimulation (Fig. 3).

1) Facilitated type (F-type): The neurons which increased discharge frequency during the stimulation.

2) Inhibited type (I-type): The neurons which decreased discharge frequency or stopped firing as the response to the stimulation.

3) Mixed type (M-type): The neurons which showed mixed response of facilitation and inhibition during the stimulation. This type involves two subgroups: inhibition preceded by facilitation and facilitation preceded by inhibition.

4) Unaffected type (U-type): The neurons which did not alter discharge frequency during the stimulation.

Among 576 neurons, 322 (55.9%) responded to RT stimulation in various manners, while other 254 (44.1%) remained unchanged. No correlation was noted between the type of response to RT stimulation and the spontaneous firing rate of MRF neuron. Number and percentage of each type of the neurons were shown in Table 1. About 31 percent of MRF neurons increased their firing rate during the stimulation, whereas about 21 percent of the neurons decreased the rate. M-type of the neurons appeared only in 3 percent.

**Table 1. Classification of the responses of reticular neurons during thalamic stimulation.**

| Type         | Number of neurons | Percentage |
|--------------|-------------------|------------|
| Facilitated (F) | 180               | 31.3       |
| Inhibited (I)  | 123               | 21.3       |
| Mixed (M)     | 19                | 3.3        |
| Unaffected (U) | 254               | 44.1       |
| Total         | 576               | 100        |

**Table 2. Effects of lidocaine and pentobarbital on spontaneous discharges of reticular neurons.**

| Drugs          | Number of MRF neurons of which firing rate was: |            |            |            |
|----------------|-----------------------------------------------|------------|------------|------------|
|                | Increased          | Decreased       | Unaffected | Total      |
| Lidocaine (2-6 mg/kg) | 14 (29%)           | 30 (61%)    | 5 (10%)    | 49 (100%)  |
| Pentobarbital (2-5 mg/kg) | 3 (8%)            | 29 (78%)    | 5 (14%)    | 37 (100%)  |
TABLE 3. Influences of lidocaine and pentobarbital on the effects of thalamic stimulation.

| Drugs          | Facilitatory effect was: | Inhibitory effect was: |
|----------------|--------------------------|------------------------|
|                | Enhanced (%)             | Unchanged (%)          | Decreased (%)          | Total (%)    | Enhanced (%)   | Unchanged (%)   | Decreased (%)   | Total (%)    |
| Lidocaine      | 9 (30%)                  | 7 (23%)                | 14 (47%)              | 30 (100%)    | 0 (0%)         | 8 (44%)         | 10 (56%)       | 18 (100%)   |
| (2-6 mg/kg)    |                          |                        |                       |             |               |                |                |             |
| Pentobarbital  | 3 (14%)                  | 6 (29%)                | 12 (57%)              | 21 (100%)    | 2 (16%)        | 5 (42%)         | 5 (42%)        | 12 (100%)   |
| (2-5 mg/kg)    |                          |                        |                       |             |               |                |                |             |

Fig. 4. An action of lidocaine on the facilitatory response to RT stimulation.

The facilitatory effect of RT stimulation (0.1 msec, 100 c/s, 8 V) on the activity of a MRF neuron was markedly diminished 2 minutes after lidocaine (2 mg/kg i.v.) whereas spontaneous discharges (before and after the stimulation) were slightly enhanced. After 30 minutes the response to the stimulation and spontaneous discharges returned to the control level.
In this experiment, 55 neurons responded particularly at the onset (on-response) or at the termination of RT stimulation (off-response). Numbers of such neurons of each type were as follow: F-type 29, I-type 11 and M-type 15. It was noteworthy that almost 80 percent of M-type neurons showed on- and/or off-response.

2. Effects of lidocaine and pentobarbital on the activities of the reticular neurons

1) Effects of the drugs on spontaneous discharges

More than 90 percent of tested neurons were affected by intravenous injection of lidocaine (2-6 mg/kg) or pentobarbital (2-5 mg/kg) (Table 2).

An inhibitory effect of both drugs on spontaneous discharges was observed in the neurons of more than 60 percent. However, these drugs were differentiated by their facilitatory effects: Lidocaine enhanced spontaneous discharge in 29 percent of the neurons, whereas pentobarbital did only in 8 percent.

![Diagram](image)

**FIG. 5.** An action of lidocaine on the inhibitory response to RT stimulation. The inhibitory effect of RT stimulation (0.1 msec, 100 c/s, 4 V) on the activity of a MRF neuron was reduced 3 minutes after lidocaine (4 mg/kg i.v.). Note the firing rate during the stimulation after lidocaine is greater than that of control in spite of slight reduction of spontaneous discharges. After 40 minutes the action of lidocaine almost disappeared.
The above-mentioned effect of lidocaine lasted 30-45 minutes after the injection, while the effect of pentobarbital lasted 90-120 minutes.

2) Influences of the drugs on the effects of thalamic stimulation

The influence of intravenous lidocaine (2-6 mg/kg) on the effect of RT stimulation was tested in 30 F-type and 18 I-type neurons (Table 3). In 14 neurons of F-type, lidocaine reduced the effect of RT stimulation. An example of such action was illustrated in Fig. 4. Lidocaine also reduced the inhibitory effect of the stimulation in 10 neurons of I-type (Fig. 5). In 9 neurons of F-type, lidocaine enhanced the effect of the stimulation. On the contrary, in I-type, no such enhanced effect was observed.

In short, lidocaine reduced the effect of RT stimulation in about 50 percent of tested F-type and I-type of the neurons. The drug enhanced the effect in 30 percent of F-type but none of I-type.

The influence of intravenous pentobarbital (2-5 mg/kg) was explored in 21 F-type and 12 I-type neurons. The effect of RT stimulation was diminished after pentobarbital in 12 of F-type and 5 of I-type neurons. On the other hand, in 3 of F-type and 2 of I-type, the drug enhanced the effect of RT stimulation.

In 16 neurons, the influences of lidocaine and pentobarbital were compared in the same neurons. Eight neurons behaved differently after the application of drugs. Fig. 6 represents an example of such neurons: Pentobarbital showed obvious reduction of facilitatory effect, whereas lidocaine potentiated the effect in spite of decrease in spontaneous discharges.

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Fig. 6. Actions of pentobarbital and lidocaine on a same MRF neuron.

Left column: The facilitatory response to RT stimulation (0.1 msec, 100 c/s, 7 V) was markedly reduced by pentobarbital (3 mg/kg i.v.).

Right column: After the action of pentobarbital terminated, lidocaine (4 mg/kg i.v.) was injected successively. Note the enhancement of facilitatory response to the stimulation by lidocaine.
The nucleus reticularis thalami (RT) was adopted here as a stimulation site of higher brain structure of which activity might strongly influence that of neurons in the midbrain reticular formation (MRF). This was based on the anatomical and physiological facts that an axonal projection from RT neuron to MRF was histologically evidenced in rats (16), and that thalamic spreading depression could influence reticular unit activity in cats (17). In our results, 56 percent of MRF neurons were affected by RT stimulation. This rate was less than we expected, but still indicated a strong influence of RT neurons upon the activity of MRF neurons.

Although pathways to influence MRF neurons are considered to be mainly descending, an antidromic response of reticular neuron can be involved in the result of RT stimulation, because the existence of ascending fibers from MRF to RT have been substantiated (18). Characteristics of antidromic response of a neuron are considered to be constancy of the latency of response (11, 19) and constant response to each pulse of higher frequency stimuli (19). In our results, however, most of responding neurons did not show such a constant response to RT stimulation. Moreover, the spontaneous discharge rate of about 40 percent of responding neurons was inhibited by the stimulation. This fact suggests that transsynaptic effect plays a leading role in our cases. Consequently, the significance of antidromic response of a neuron appears to be minor in this study.

In the present experiment, systemic administration of a small dose of lidocaine (2–6 mg/kg) or pentobarbital (2–5 mg/kg), elicited some modulation of single unit activity of MRF neuron. However, the nature of action of lidocaine on the neuron activity appeared somewhat different from that of pentobarbital. On the spontaneous discharges of reticular neurons, similar inhibitory effects of lidocaine and pentobarbital were obvious, but as to their facilitatory effect, lidocaine enhanced the discharges in 29 percent of the neurons whereas pentobarbital enhanced only in 8 percent. We speculate that the neurons of which spontaneous discharges were enhanced by these central nervous depressants, might be under rather strong regulation of an inhibitory neuronal system in physiological states, and that the blocking effect of these drugs on inhibitory system caused an enhancement of spontaneous discharges in these neurons. Above mentioned discrepancy between the effects of lidocaine and pentobarbital may be due to the difference of sensitivity between excitatory and inhibitory neurons to lidocaine as Tanaka and Yamasaki (20) reported in the rabbit's cortex and de Jong et al. (21) observed in monosynaptic reflex of spinal cord in cats.

These drugs also modified the effects of RT stimulation on MRF neuron activities. In F-type of MRF neurons, lidocaine enhanced the facilitatory response in 30 percent of tested neurons, whereas pentobarbital enhanced it in 14 percent. In I-type of MRF neurons, no enhancement of inhibitory response was observed following injection of lidocaine, and instead, decreased inhibitory effect was exerted in 56 percent. Pentobarbital also decreased the inhibitory effect in some neurons, and this disinhibitory action had been described by Valdman (22) in a MRF neuron of which activity was inhibited by gluteal
nerve stimulation. Since enhancement of facilitatory response by a central nervous depressant drug is considered to be owing to a selective blocking effect of the drug on inhibitory neurons (23), it may be said that enhancement of facilitatory effect and decrease of inhibitory effect have a common "excitatory" mechanism in the brain. Analogously, decrease of facilitatory effect and enhancement of inhibitory effect are regarded as concurrently "depressive".

As shown in Table 4, which is revised from Table 3, the ratio between "excitatory" and "depressive" effect is much higher in lidocaine than pentobarbital. Analogous results are obtained in the experiment of 16 neurons which were subjected to the test of lidocaine and pentobarbital concomitantly. In a half of them lidocaine showed "excitatory" effect and pentobarbital "depressive" effect. Thus the hypothesis proposed by Tanaka and Yamasaki (20) that lidocaine blocks inhibitory neurons more easily than excitatory ones in the cortex, seems to be applicable also to reticular neurons.

**Summary**

In unanesthetized rats, 576 single unit activities of midbrain reticular formation (MRF) were picked up with extracellular tungsten microelectrodes. Fifty-six percent of MRF neurons were affected by stimulation of nucleus reticularis thalami (RT) in various manners: Facilitated, inhibited and mixed. This fact suggests that RT neurons strongly influence the activities of MRF neurons.

Intravenous injection of lidocaine (2-6 mg/kg) reduced the spontaneous firing rate in 61 percent and increased in 29 percent of MRF neurons. Pentobarbital (2-5 mg/kg) reduced the firing rate in 78 percent and increased only in 8 percent.

Influences of lidocaine and pentobarbital on the effects of RT stimulation were also studied. Lidocaine and pentobarbital decreased both facilitatory and inhibitory effects in almost 50 percent of the neurons. Lidocaine enhanced the facilitatory effect in 30 percent of the cases, whereas pentobarbital enhanced only in 14 percent. Moreover, pentobarbital enhanced the inhibitory effect of RT stimulation in 16 percent, whereas no such a case was observed after lidocaine.

These facts may indicate that both drugs have blocking actions on excitatory and inhibitory neurons but lidocaine blocks inhibitory ones more easily than pentobarbital.
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