

# Differential Effects of Anesthetics on Mesencephalic Reticular Neurons:

## II. Responses to Repetitive Somatosensory Electrical Stimulation

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The differential effects of anesthetics on unitary behavior of the cat's mesencephalic reticular formation in response to repetitive electrical stimulation of the skin were studied by means of long-term microelectrode recording and computer analysis. In most units the anesthetics decreased the total number of firings in response to repetitive electrical stimulation of the skin. However, the ratio of evoked to spontaneous activity varied from unit to unit. Generally, the ratio was highest with sodium thiopental, and lowest during diethyl ether anesthesia. Evoked activity was easily distinguished from background activity during sodium thiopental and halothane anesthesia, but hardly distinguishable during diethyl ether anesthesia. The poststimulus times of short-latency discharges were hardly affected by the anesthetics in most units until the units ceased to respond to stimulation. In contrast, long-latency discharges were easily affected by anesthetics. (Key words: Mesencephalic reticular formation units; Nitrous oxide; Diethyl ether; Halothane; Sodium thiopental.)

THE COMPANION STUDY<sup>1</sup> has shown that although in most units in the mesencephalic reticular formation (MRF) spontaneous firings decrease in response to anesthetics, there are some units in which firing rates increase. Although susceptibility of the units to anesthetics varies widely from unit to unit, there are two types of spontaneous firing patterns in relation to anesthesia, the "grouped" and "tonic" types. There are some differential effects of anesthetics on the activities of the units in the MRF.

In the present study the behavior of the units in the MRF in response to repetitive electrical stimulation of the skin has been ex-

plored further, using long-term microelectrode recording and computer analysis.

### Methods

Experimental arrangements and procedures are described in the preceding paper.<sup>1</sup>

Electrical stimulation of the skin was delivered through a pair of stainless steel hypodermic needles inserted subcutaneously. The effectiveness of stimulation was tested on the cat's four paws and the most effective site was chosen for a long series of stimulations. The frequency of stimulation was set from 1 to 4 cps. The stimulus was a 0.5-msec square pulse of 50 v.

The responses of the units were analyzed by means of a digital computer (CAT 400B and Control Data 3200) after the experiments. The number of spikes in a fixed time interval (FC) and the poststimulus time histogram (PSTH) were computed. The averaged somatosensory evoked potentials from the scalp were computed and plotted simultaneously.

### Results

Most of the units (67 of 83) responded to electrical stimulation applied to wide areas of body surface with increases in firing rates. There were only two units (2/83) in which discharge rates decreased with electrical stimulation of the skin. The rest (14 units) did not respond to the stimulation. It was frequently demonstrated that the units, particularly those in the so-called boundary area between the MRF and the colliculus superior, responded to both photic stimulation and electrical stimulation of the skin.

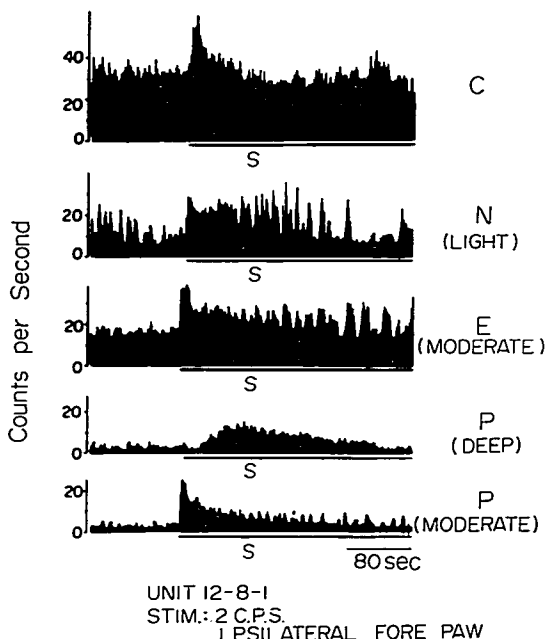
Most units responded to the electrical stimulation with burst discharges, but the numbers of spikes following stimulation and the latencies of the first spikes varied widely from unit to unit and also from time to time during a train of repetitive stimulation. Moreover, the

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FIG. 1. The response patterns of one MRF unit to a train of repetitive electrical stimulations (S) of the skin during wakefulness and anesthesia, shown by FC. This unit responds to stimuli in a rapidly-augmenting fashion during wakefulness (C), the light stage (75 per cent) of nitrous oxide (N) anesthesia, and the moderate stages of ether (E) and sodium thiopental (P) anesthesia. On the other hand, the unit responds to stimuli in a slowly-augmenting fashion during the deep stage of thiopental anesthesia.



responsiveness and fading (attenuation) of the units elicited by the repetitive stimuli varied widely. A few units (3/67) responded to each stimulus with one spike.

#### NUMBER OF SPIKES IN A FIXED TIME INTERVAL (FC)

*Patterns of responses to stimulation:* There were two types of response to repetitive stimulation in the unanesthetized cat. Some units responded to a train of stimuli in a rapidly augmenting fashion, reaching a peak within a few subsequent stimuli, and then attenuated slowly. The other units responded in a slowly-augmenting fashion, reaching a peak after more than ten subsequent stimuli, and attenuated slowly. Of 26 units tested, 11 units showed the former and the rest, the latter type of response during the unanesthetized state.

With administration of anesthetic drugs, the patterns of responsiveness to repetitive stimu-

lation became more complex. The patterns sometimes also changed in type during the course of anesthesia. This lack of uniformity in the response patterns elicited by repetitive stimulation during anesthesia was a characteristic feature. Although this was the case, it was consistently found that the very-slowly-augmenting response was present during the deep stage of sodium thiopental anesthesia (fig. 1).

*Changes in responsiveness to stimulation:* In most units (62 of 67), the total numbers of spikes in response to trains of repetitive stimulation decreased during the deep stage of anesthesia with each anesthetic, with a simultaneous decrease of spontaneous discharges (fig. 2A). During light or moderate anesthesia with each anesthetic, most of the units (60 of 62) also showed decreases of evoked discharges in response to repetitive stimulation. In two units, however, the number of spikes elicited by stimulation increased to a

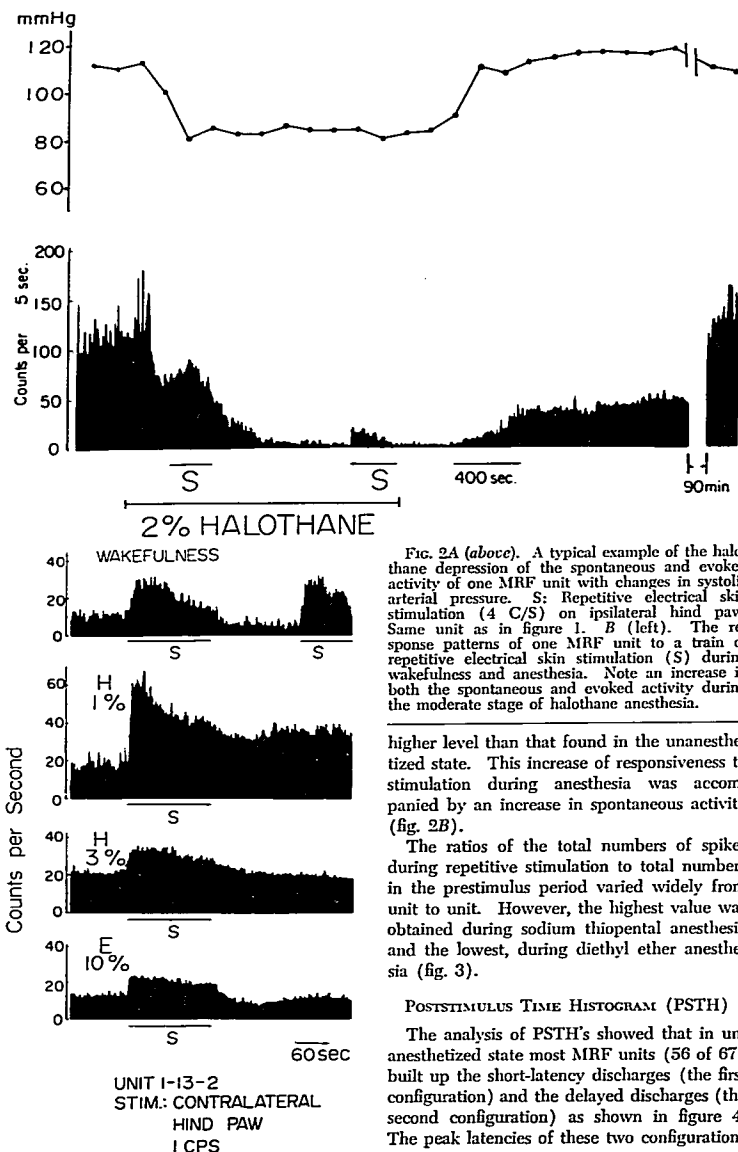


FIG. 2A (above). A typical example of the halothane depression of the spontaneous and evoked activity of one MRF unit with changes in systolic arterial pressure. S: Repetitive electrical skin stimulation (4 C/S) on ipsilateral hind paw. Same unit as in figure 1. B (left). The response patterns of one MRF unit to a train of repetitive electrical skin stimulation (S) during wakefulness and anesthesia. Note an increase in both the spontaneous and evoked activity during the moderate stage of halothane anesthesia.

higher level than that found in the unanesthetized state. This increase of responsiveness to stimulation during anesthesia was accompanied by an increase in spontaneous activity (fig. 2B).

The ratios of the total numbers of spikes during repetitive stimulation to total numbers in the prestimulus period varied widely from unit to unit. However, the highest value was obtained during sodium thiopental anesthesia and the lowest, during diethyl ether anesthesia (fig. 3).

#### POSTSTIMULUS TIME HISTOGRAM (PSTH)

The analysis of PSTH's showed that in unanesthetized state most MRF units (56 of 67) built up the short-latency discharges (the first configuration) and the delayed discharges (the second configuration) as shown in figure 4. The peak latencies of these two configurations

varied from unit to unit, and also depended on the site of stimulation. The rest of the units (11 of 67) showed only one configuration each, of various latencies. Following administration of anesthetics, these discharges were depressed and became indistinct from the background activity, i.e., units began to fire independently of stimuli. Susceptibility of the delayed discharges to anesthesia was greater than that of the short-latency discharges in all units. The peak latency of the first configuration was hardly affected by any anesthetic agent, while the second configuration tended to shift to the right and changed its form (fig. 4). This tendency was clearly evident during sodium thiopental and halothane anesthesia, that is, units showed high responsiveness to stimulation in spite of profound depression of spontaneous activity (fig. 4, bottom right). Consequently, configurations of the first and delayed responses became distinguishable from those of the background activity. In contrast to this, during diethyl ether anesthesia the configuration became lost in the background activity (fig. 4, upper right).

### Discussion

The characteristic features of the polysensory and convergent modalities of MRF units, reported by several authors,<sup>2-4</sup> were frequently noticed during the procedures of this experiment.

The fact that the poststimulus time of the "first configuration" was unchanged by the administration of anesthetics with concomitant depression and prolongation of the "delayed configuration" may coincide with the results obtained by gross electrode studies.<sup>5-7</sup> This fact also suggests that the state of anesthesia may not be caused by particular kinds of units, but may be caused by the functional state of the units. The general tendency in evoked activities of units in the MRF is: the longer the latency of responses, the greater the susceptibility to anesthetics.

In most units, total numbers of firings in response to repetitive electrical stimulation were decreased by the anesthetics. However, during halothane anesthesia and sodium thiopental anesthesia evoked activity frequently was well maintained in spite of profound decreases in spontaneous activity. This high responsiveness of the MRF units to stimulation, with the tendency to fire in "groups,"<sup>1</sup> during halo-

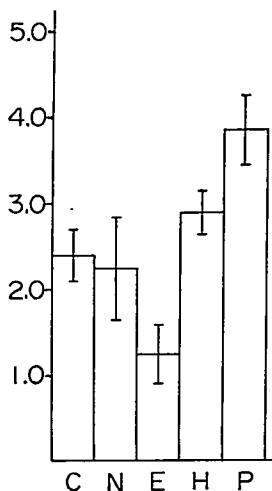


FIG. 3. The ratios of the numbers of spikes during repetitive stimulation to the prestimulus numbers during wakefulness (C), the light stage of nitrous oxide anesthesia (N), and the moderate stages of diethyl ether (E), halothane (H), and thiopental (P), anesthesia. Means and standard errors were computed for 30 seconds immediately before and after the onset of stimulation in eight units of MRF. Mean values are significantly different from each other ( $P < 0.05$ ), except when control and nitrous oxide anesthesia values are compared ( $P > 0.1$ ).

thane and sodium thiopental anesthesia, must have something to do with more hypnotic and less analgesic actions of these two drugs often seen in clinical anesthesia. Conversely, the relatively low responsiveness of MRF units to stimulation, with the tendency to fire in tonic fashion<sup>1</sup> during ether anesthesia and nitrous oxide anesthesia might be responsible for some neuronal mechanisms by which these two drugs exert more analgesic actions.

Anesthetics enhanced the attenuation of unit responsiveness to repetitive electrical stimulation of the skin in most units. However the degrees and times to onset of the attenuation varied from unit to unit.

The striking feature of the deep stage of thiopental anesthesia, i.e., the very-slowly-augmenting responses, remains unexplained. Conceivably, the activity of inhibitory loops, which are thought to be partly responsible for the development of the attenuation,<sup>5</sup> may be

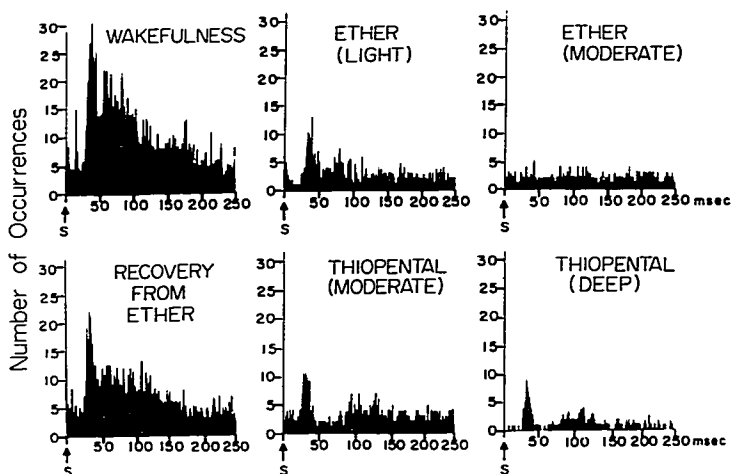


FIG. 4. PSTH's of one MRF unit during wakefulness, diethyl ether anesthesia, and sodium thiopental anesthesia. Both short-latency and long-latency discharges are hardly distinguishable from the background activity at the moderate stage of diethyl ether anesthesia. In contrast, both types of discharges are clearly distinguishable from the background activity during sodium thiopental anesthesia, even at the deep stage (same unit as in fig. 1).

depressed by large doses of sodium thiopental, and the facilitatory loops may become activated in the course of repetitive stimulation. It is not feasible to comment on the question of whether the enhancement of the cortical recruiting response or that of the secondary response during barbiturate anesthesia<sup>6,7</sup> is due to the same mechanism as the slowly-augmenting-response of the MRF units in the present study. The lack of uniformity in evoked responses of units in the MRF might be a characteristic distinction from the lemniscal system. Such great variation in evoked responses of the MRF was also observed in the recovery cycles of gross responses by Boyd.<sup>8</sup> Finally, it should be mentioned that the anesthetic state is not a simple neuronal depression, but a complex depressed state, when viewed at the unit level of the MRF.

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