# PHYSIOLOGY

## THE INHIBITORY INFLUENCE OF THE BULBAR RETICULAR FORMATION AND ITS INFLUENCE ON THE SPINAL CORD

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Since the initial work of I. M. Sechenov [2], a large number of investigations of the influence of the subcortical areas of the brain on the spinal cord and on motor activity generally have been carried out [1, 3, 6, 8, 13, etc.].

The work of Magoun and his co-workers [10, 11] has done much to stimulate interest in this problem. Using anesthetised and decerebrate preparations, they demonstrated the existence of a median region whose stimulation produced inhibition, and a lateral area which caused facilitation of spinal reflexes. They also found a facilitatory area of considerable extent in the diencephalon and mesencephalon. Many workers have subsequently, and quite rightly, critized Magoun's views on the exclusively generalized nature of the inhibition and facilitation. Thus, many of them [5, 16, and others], besides obtaining generalized inhibitory and facilitatory effects, have also found motor reactions involving reciprocal innervation, as well as various influences on mono- and polysynaptic reflexes. It appears that the reciprocal reaction is more typical of the stimulation of the reticular formation than is the inhibitory or facilitatory influence which, according to these authors, occurs only under conditions of reduced nervous activity resulting, for instance, from the action of anesthetics, or from the decerebration operation.

Recently, Mandell and Bach [12], in experiments with electrodes implanted in the medial reticular formation, have shown that the inhibitory effects on spinal reflexes can be observed only under anesthesia. Neither before or after the anesthetic, could any inhibition of these reflexes be obtained. Under these conditions, only movements of a more or less complex character were elicited.

According to the most recent information concerning the function of the reticular formation, many central processes concerned in both normal and pathological motor activity may be considered from the point of view of the relations between regions of the brain stem which are known either to inhibit or to facilitate activity in the cord. For this reason, these problems deserve careful investigation. Is the inhibitory effect of the reticular formation on spinal cord activity the result of an artificial reduction, through the action of anesthesia, or surgical interference of the general functional condition of the brain, or does it occur under normal conditions ? We have undertaken the present investigation in order to solve this problem.

### METHOD

The experiments were carried out on 15 adult cats under various depths of ether or chloralose anesthesia; for chloralose, we used from 5 to 60 mg/kg; experiments were also carried out without anesthesia, $1\frac{1}{2}$-2 hours after an operation performed under ether. The quadriceps and semitendinosus muscles were prepared for recording, the peroneal nerve was stimulated, usually once per second; the skull was opened from behind for stimulation of the reticular formation of the medulla and midbrain. In some experiments, the cerebellum was removed, and in others it was preserved. The reticular formation was stimulated at a frequency of 150-300 shocks per second, and at a voltage of 0.5-5v, the duration of the stimulus being 0.5-1 milliseconds; bipolar electrodes

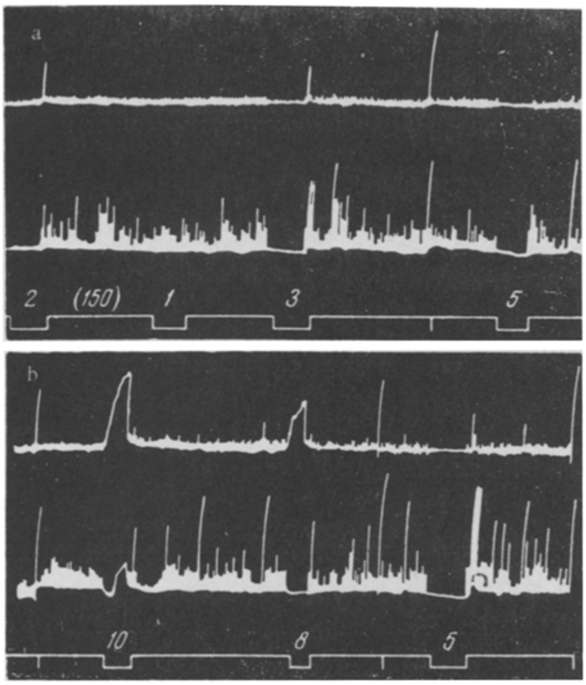


Fig. 1. Effect of stimulation of the medial region of the bulbar reticular formation on reflex contractions under ether anesthesia (10 minutes after administration of ether was stopped).
Curves, from above downwards: contractions of the quadriceps and semitendinosus muscles. Bottom line) depression of the trace indicates onset of stimulation of brain. Figures outside brackets and over the trace indicate the applied voltage, figures in brackets represent the frequency. There is a well-marked generalized inhibition (of both antagonists) which develops at a stimulus of 2 and 3 v. Facilitation of the reflex contractions occurring at the end of the stimulus is also quite well shown. With stronger stimuli of 8 and 10 v, a tonic contraction of the muscles occurs.

having a tip diameter of 20-25μ were used, and the distance between them was 0.5 mm; they were placed in position by means of a stereotactic apparatus. From time to time, the effects of stimulation applied to the facilitatory or inhibitory regions of the reticular formation were superimposed on the rhythmical reflex contractions.

## RESULTS

### 1. Experiments Using Ether Anesthesia

If, immediately after administering the ether, when the animal is still fairly deeply anesthetized, a pair of electrodes are introduced into the medial bulbar reticular formation (an area which inhibits activity in the cord), and another pair into the mesencephalic or pontile tegmentum or into the lateral part of the bulbar reticular formation (facilitatory region), then it can easily be seen that even with weak stimuli, inhibition (Fig. 1), or facilitation (Fig. 2, b, c) of the reflex contractions are readily obtained.

In the case of small stimulating voltages at a low frequency, inhibition is obtained much more readily than facilitation. Also, the zone from which an inhibitory effect is obtained appears to be greater in extent, inhibitory points are easily found, while much searching is required to discover facilitatory ones.

Even when the animal is beginning to recover from the anesthetic, if a slight increase of stimulation to an inhibitory area is given, it is often possible to observe, in addition to the suppression of the reflex contractions, the development of tonic contractions, usually of a reciprocal type, in one or both of the muscles from which the recordings are made (see Fig. 1, Fig. 2, b, c).

As the animal recovers from the anesthetic, first of all, the regular reflex contractions which have been occurring up till now under the influence of the anesthetic, become disturbed: in response to rhythmic stimulation of the peroneal nerve, the contractions show great variations in amplitude — at times being abnormally strong, and at others not occurring at all. Also, the inhibitory points are missing. The part of the brain whose stimulation under ether previously inhibited reflex contractions now exerts no inhibitory influence (see Fig. 2,a); stimulation of neighboring points is also without any inhibitory effect.

Stimulation of the mesencephalic facilitatory region at this time is almost as effective as before, and with strong stimuli, tonic contractions of the muscles are readily evoked (see Fig. 2,b,c). When the effect of the anesthesia has worn off, it is very difficult to obtain a "pure" facilitation (i.e. an increase in amplitude of the reflex contractions without a tonic component); usually, any weak stimulus applied to those points, which at a certain depth of ether anesthesia brought about only an increase in the amplitude of the reflex contractions, now evokes movements, usually in both muscles and for the most part of the reciprocal type.

### 2. Experiments With Chloralose Anesthesia

In some experiments, 1½-2 hours after ceasing to administer the ether, and after a detailed study of the effect of applying stimuli to different parts of the bulbar and mesencephalic reticular formation, small repeated

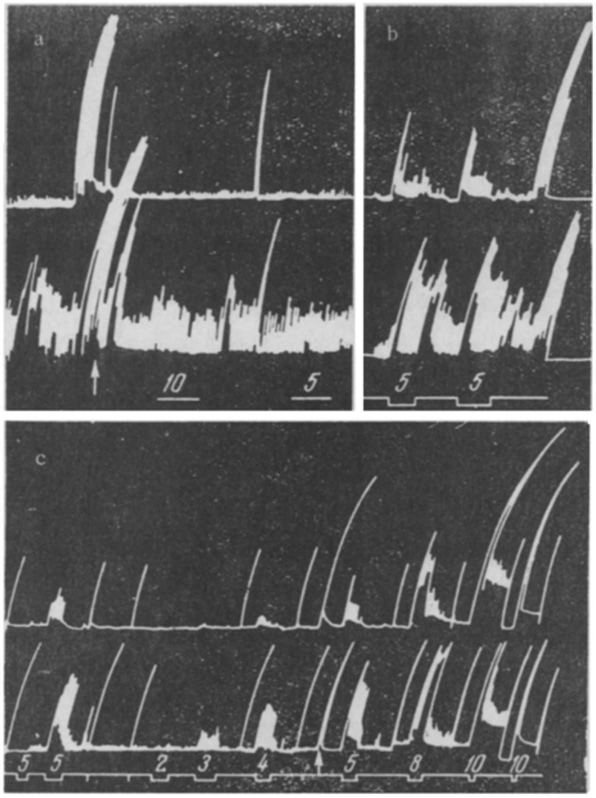


Fig. 2. Effect of stimulation of the mesencephalic and bulbar reticular formation on reflex contractions after recovery from ether anesthesia (same preparation $1\frac{1}{2}$ hours after administration of ether was stopped). Recordings from muscles as in Fig. 1. a) Stimulation (horizontal lines under the curves) of the same inhibitory portion of the bulbar reticular formation as in Fig. 1; there is now no inhibitory effect; b) stimulation of the mesencephalic (facilitatory) area; facilitation with tonic contraction; c) 20 minutes later a further stimulus is applied to the same facilitatory area with different stimuli strengths; the arrow indicates spontaneous movements of the animal.

doses of 5 mg/kg were given intravenously at intervals of 15-20 minutes. Between injections, the effect on the reflex contractions of stimulating many different points in the reticular formation was investigated. In another set of experiments, step by step injection of the chloralose was carried out as follows. While the animal was under fairly deep ether anesthesia, the areas in the mesencephalon and bulbar reticular formation which gave clearly shown facilitatory and inhibitory effects on the reflex contractions were identified. The electrodes were then left in these positions, the animal was allowed to recover from the ether anesthesia, and the effects of stimulating these points was again found. (The results of this operation have been described above). Chloralose was then injected in doses of 5 mg/kg, or alternatively the depth of anesthesia was immediately brought up to the required level by giving 20-25, 35-40, or 50-60 mg/kg of chloralose. The object of all these experiments was to find what dose of anesthetic was required to enable well-marked inhibitory effects to be obtained from the bulbar reticular formation. At the same time, a study was made of the effects of stimulation of the mesencephalic facilitatory area.

The experiments showed that with doses up to 15-20 mg/kg, the effect of stimulating the inhibitory region was the same as was described for the period when the animal was recovering from the ether; in other words, the reflex contractions were irregular, tonic contractions were frequently observed, and there was no inhibition of the spinal reflex. Only with doses of 15-20 mg/kg and above do the reflex contractions become regular, and at this time the inhibitory effect of stimulation of the medial bulbar reticular area becomes manifest.

Thus, according to Sprague and Chambers [16], and Mandell and Bach [12], it is true that a certain level of anesthesia is, indeed, necessary in order to demonstrate the inhibitory effect of the bulbar reticular formation. Below this level, there is usually no inhibitory effect, and frequently stimulation of these points produces tonic motor effects.

These results would appear to show that in the nonanesthetized animal, no inhibitory effect of the reticular formation is observed under normal conditions, and that such an effect is to some extent brought about by a certain deterioration of the condition of the brain under the influence of the anesthetic. However, we must enquire what it is that occurs under the anesthetic; it could be that a new phenomenon takes place which is not found under normal conditions, or alternatively it might be that a certain level of anesthetic represents the conditions necessary for the development of a phenomenon which, under normal conditions, is masked by other processes of an opposite kind, occurring at the same time.

Some information on this question is obtained from experiments in which, besides making observations on the inhibitory effect and its relation to the depth of anesthesia, we made a simultaneous study of the facilitatory effect of the mesencephalic reticular formation. These experiments showed that when the inhibitory effect was

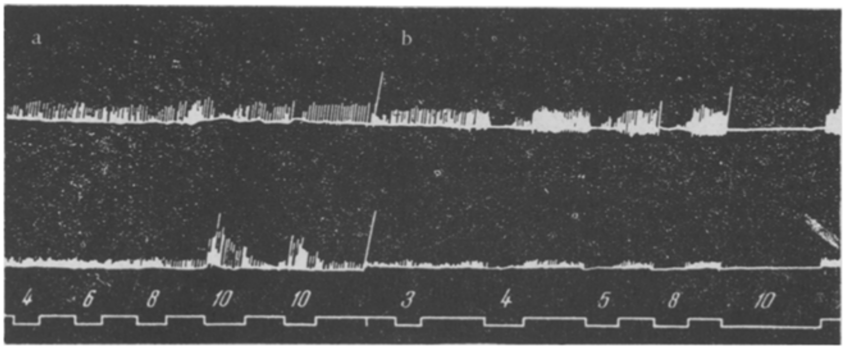


Fig. 3. Marked relaxation and change in the facilitatory effect of the mesencephalic reticular formation on deepening chloralose anesthesia (same preparation as in Fig. 2; chloralose - 35 mg/kg). a) Stimulus strengths of 3, 4, and 5 v, which before anesthetizing caused a well-marked facilitation of reflex contractions (see Fig. 2, b) now cause no such reaction; weak facilitation, showing a marked reduction on repeating the stimulus, occurs only at a stimulus of 10 v; also, facilitation is observed only in the flexors, while the extensors simultaneously suffer a short transient inhibition; c) generalized inhibition occurs in full strength, but without subsequent facilitation.

maximally developed, the facilitation induced by stimulation of the mesencephalic reticular formation was considerably reduced and finally vanished; at the same time it sometimes changed from a generalized facilitation to producing a reciprocal effect (Fig. 3,a). The inhibitory effect is maintained considerably longer, until the depth of anesthesia is deeper (50-60 mg/kg and above), with hardly any reduction, and only when the anesthesia is still deeper is the activity in the cord reduced, or even eliminated.

It may therefore be supposed that the absence of inhibition by the bulbar reticular formation in nonanesthetized animals is due to the simultaneous tonic facilitatory effect of the reticular formation of the midbrain; this effect must be supposed to preponderate and so to prevent the manifestation of the inhibition. In the waking condition, especially during the early stages of anesthesia (at any rate judging by the increasing "activating" effect of the reticular formation on the electrical activity of the cerebral cortex), clearly, we are dealing with a state of strong excitation of the mesencephalic facilitatory region. From here a large number of impulses, which, as far as their motor effect is concerned are subthreshold, must pass along the ventrolateral columns of the cord [4, 14] to groups of internuncial and motor neurones, and so bring about a state of heightened excitability which hinders the manifestation of inhibitory effects. This may be due to the fact that at this time, any weak stimulus, even one applied to the inhibitory area of the medulla, first of all elicits tonic muscular contractions. However, as the effect of the anesthetic increases, the facilitatory influence of the mesencephalic region becomes reduced, the neurones of the spinal cord are to some extent freed from the constant facilitatory impulses, and it becomes possible for the weaker inhibitory effects from the bulbar region to develop.

Thus, it must be possible for the reticular formation to exert a generalized inhibitory influence under normal conditions. It evidently takes part in various coordinated movements and behavior patterns, and may be of considerable importance, as when standing on guard, when, together with the "activation" of the cortex, the animal can be seen to stand in a fixed position. However, in most cases the inhibitory effect is considerably weaker than the facilitatory one. For it to be manifested, it is necessary that there should be some reduction or limitation of the descending facilitatory influence of the reticular formation, which can be obtained by the appropriate depth of anesthesia (see also [15]), or by a transsection in the mesencephalic facilitatory area; in order to demonstrate the ascending "activating" influence of the reticular formation on the electrical activity of the cortex, it is again necessary to produce a state of slow activity, and this is obtained by injecting a small dose of anesthetic, or by natural sleep. However, this does not constitute a reason to deny the importance of the ascending "activating" system under normal conditions of existence, or to doubt that such an influence does in fact exist.

## SUMMARY

Experiments were performed on intact cats. The authors studied the changes of the effects of direct electrical stimulation of mesencephalic facilitatory and of bulbar inhibitory areas onthe rhythmic reflex of antagonists associated with development of ether and chloralose anesthesia.

Experiments demonstrated that distinct generalized inhibition of antagonists, which is observed in condition of ether anesthesia, disappears in 1.5-2 hours after the interruption of anesthesia. At this time the facilitatory effect which is frequently associated with a tonic contraction is still pronounced. If the anesthesia is deepened gradually or at once (by intravenous injection of chloralose) the generalized inhibition of the reflex quivering is again manifested to its full extent after the administration of 15-20 mg/kg of body weight. At the same time the facilitatory effect of the mesencephalic reticular formation is greatly weakened. The inhibitory effect of the bulbar reticular formation appeared to be more resistant to anesthesia: it weakens and disappears only with the large concentrations of the drug (50-60 mg/kg and more).

All this points to the following: 1) the mesencephalic facilitatory and the bulbar inhibiting areas possess different sensitivity and resistance to anesthetics, 2) the inhibitory effect of the reticular formation of the brain stem in nonanesthetized animals is obscured by its more significant facilitating effect on the spinal cord.

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