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Abstract

In decerebrated cats the impulse discharges were detected by means of an unipolar micro-electrode from a single inspiratory neuron in the respiratory centers, and the change in discharge produced by administration of stimulating, as well as depressant agents, was studied. The results were summarized as follows. 1) Inhalation of the air containing all. excess of carbon dioxide, as well as the air deficient of oxygen and the intravenous administration of a small dose of caffeine, aminocordine and lobeline produced a) a remarkable increase of frequency of impulses in the stage of constant frequency of the volley, b) a rapid increase of frequency of impulses in the stage of crescent frequency of the volley and c) a shortening of the duration of the volleys, as well as of silent periods. 2) In narcosis by a moderate dose of morphine, as well as in the recovery stage from apnea produced by over-ventilation, there were observed the phenomena which were exactly opposite to those described in 1). 3) It was concluded that a most essential sign by which one can discern whether the activity of the respiratory Genters is raised or depressed, is the changes of the frequency of impulses produced from an inspiratory neuron. The expense of this research was defrayed from the grant in aid of the Ministry of Education.

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ON THE EXCITATION AND INHIBITION OF THE INSPIRATORY NEURON IN THE RESPIRATORY CENTERS

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When the respiartory movements are studied by means of a mechanogram, the investigators have paid special attention to changes of frequency, depth and minute volume of breathings. Needless to say, the changes above mentioned were secondarily evoked by those of the activity of the respiratory centers, the study of which has been, however, because of lack of appropriate techniques only rarely performed, although the activity of phrenic as well as intercostal neurons has been studied extensively by *Pitts*[13], *Bronk* and *Ferguson*[4] and many other investigators[1) 7) 11) 16)]. We know now that the action potentials or impulse discharges detected from the region of the respiratory centers can be fairly adopted as the index of the activity of the respiratory centers[2) 5) 6) 8)]. We have recently studied the changes of discharges in the respiratory centers, which were caused in some respiratory reflexes[9) 10)]. In the following experiments we observed what changes would be elicited in impulse discharges of the centers when the well known respiratory stimulants or depressants were administered to experimental animals. The results are reported in the following.

Methods

As experimental animals cats were used. The animals were first lightly anesthetized with 0.1 g. of urethane per kilogram body weight and then decerebrated. As the index of the activity of the respiratory centers, the discharges were detected by means of an unipolar microelectrode inserted into the region of the normal respiratory centers. As regards the techniques of the decerebration and recording of the action potentials, the details were described in the previously published report[8)]. In

the experiments in which the effects of the excess and deficiency of carbon dioxide as well as of the deficiency of oxygen upon the centers were studied, three sorts of gases, i. e., CO_2, O_2 and N_2, were each transmitted through a gasmeter into a tank of spirometer type, the capacity of which is 150 litres. The accurate percentages of CO_2 and O_2 were measured by means of *Haldane*'s gas analysis apparatus. The mixed gases mentioned above were breathed through the one valve into the lungs, while the expired air was breathed through the other valve out to the outer air. The agents [3) 12) 15)] for stimulating or depressing the respiratory centers were injected into the saphenous vein.

Results

The effects of the content of carbon dioxide in the inspired air upon the discharges of the inspiratory neuron :— The excess of carbon dioxide in the inspired air increases remarkably the rate and amplitude of breathing as already described by *Scott*[14]. In that case the inspiratory discharges change as follows.

a) In the stage of crescent frequency the impulses successively increase their frequency more rapidly than in the normal volley and one can see, consequently, on the mechanogram that the gradient of the inspiratory phase is larger than that in the normal breathing. These phenomena become more and more pronounced with the time elapsed after breathing the air concerned. These facts are noticed when one compares the normal volley in fig. 1, A with the volleys in fig. 1, B, C and D.

b) The frequency of impulses increases remarkably in the stage of constant frequency. In the example shown in fig. 1 the frequency of impulses in the stage described is 43/sec. in normal volley, while it increases rapidly in the course of time after breathing the air containing the excess of carbon dioxide, i. e., it is 65/sec., 80/sec. and 100/sec. respectively, 45, 90 and 130 seconds after breathing the air described above. According to *Pitts*[13] similar results are obtained by rebreathing in phrenic neuron of cat.

c) The duration of the volley, as well as the silent period (the period between two successive volleys), shortens in general. But a volley with a prolonged duration may be only rarely inter-

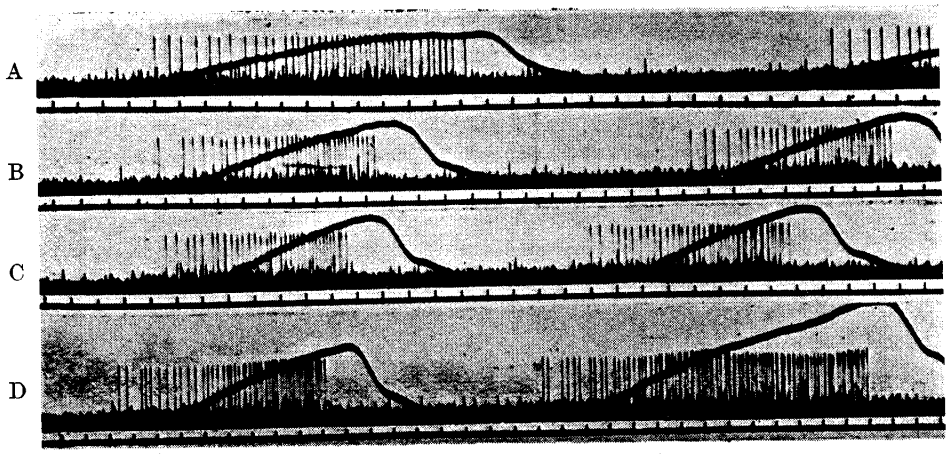

Fig. 1. The effect of CO_2 excess upon the discharges of a single inspiratory neuron. Cat breathes the air containing 15.8% CO_2, 22.3% O_2 and N_2. A. normal volley. B, C and D show the volleys observed 45, 90 and 130 seconds respectively after breathing the gas concerned. In the mechanogram inspiration upwards. Time marks 1/12 sec..

polated, as shown in the second volley in fig. 1, D.

d) The total number of impulses in one volley is generally a little less or a little more than that in the normal volley, because the increase of frequency of impulses goes almost always hand in hand with the decrease of duration of the volley. The rare case in which the total number of impulses is increased remarkably is shown in fig. 1, D.

When, having been produced the apnea by hyperventilation, the ventilation is stopped, the breathing reappears sooner or later. The course of the discharges is shown in fig. 2. The discharges begin to be produced continuously and irregularly with much lower frequency than in the normal volley. The frequency is at first gradually and then rapidly increased, approaching that of the normal volley and being followed by a silent period (fig. 2, D).

The succeeding discharges constitute evidently the volleys (fig. 2, E and F) in which the frequency of impulses is, however, yet lower than that of the normal volley. In the next volley, finally, the behavior of impulses is almost the same as that of the normal (fig. 2, G). We are interested in the phenomena described above, because they reveal the recovery process of the centers from their depressed state.

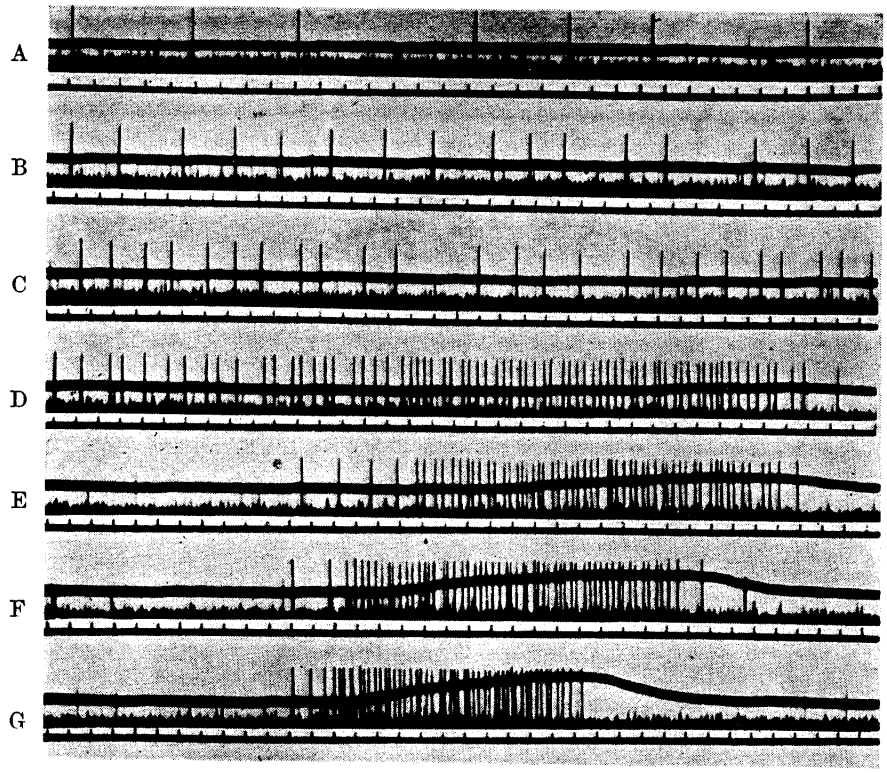

Fig. 2. Discharges of a single inspiratory neuron in the stage of recovery from the apnea produced by the hyperventilation.
Cat (3kg.) decerebrated. A—G show the change of discharges successively with the time elapsed after stopping the over-ventilation. Explanations in text. Time marks 1/12 sec..

The effects of the content of oxygen in the inspired air upon the discharges of the inspiratory neuron :— If the percentage of oxygen in the inspired air is decreased to about half its normal amount, there is always a considerable increase in frequency of impulses, while the duration of the volley, as well as the silent period, is at first rather slightly prolonged (fig. 3) and then gradually shortened in the course of time. If the amount of oxygen is further decreased, the excitatory effects described above become more remarkable (fig. 4).

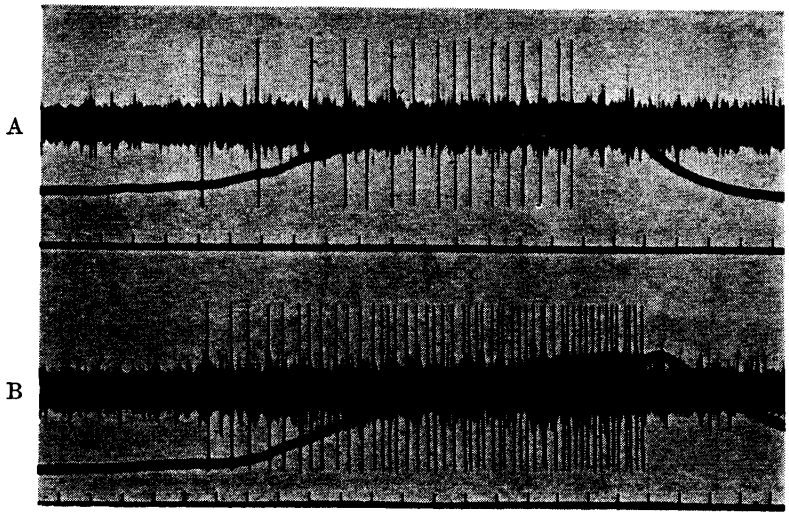

Fig. 3. Effects of oxygen lack upon the discharges of a single inspiratory neuron.
Cat (2.5 kg.) breathes the air containing 11.1% O_2. A. Normal volley. B. 30 seconds after breathing the air concerned. The frequency of impulses increases remarkably. Time marks 1/12 sec..

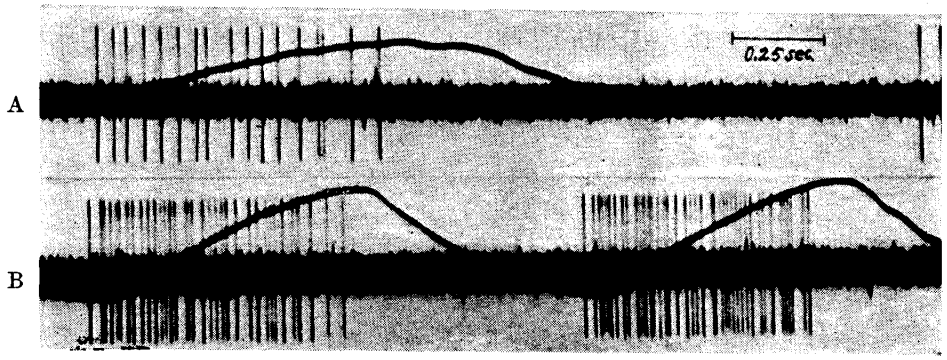

Fig. 4. Effects of oxygen lack upon the discharges of a single inspiratory neuron.
Cat breathes the air containing 6% O_2. A. Normal volley. B. 30 seconds after breathing the air concerned.

The effects of caffeine upon the discharges of the inspiratory neuron :— When 0.5—1.0 cc. of 5% caffeine solution is administered intravenously, the rhythm and depth of breathing is, as is well known, remarkably increased. As shown in fig. 5 the duration, as well as silent period of the inspiratory volley, is shortened and the frequency of impulses is considerably in-

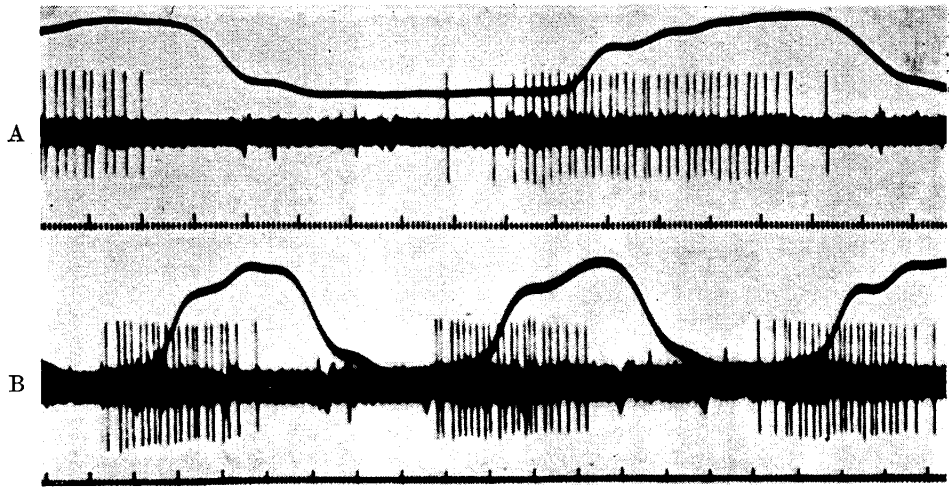

Fig. 5. Effects of caffeine upon the discharges of a single inspiratory neuron. Cat (3.5 kg.) decerebrated. 1.0 cc. of 5% caffeine solution (14mg/kg.) administered intravenously. A. Normal volley. B. 30 seconds after administration of caffeine.

creased. In the example shown the frequency of the normal volley is 68/sec. and increases to 80/sec. after administration of caffeine. These results are similar to those produced by an excess of carbon dioxide.

The effects of aminocordine upon the discharges of the inspiratory neuron :— When 0.10—0.15 cc. of 25% aminocordine is intravenously administered, impulse discharges are at first somewhat irregular and differ from the normal pattern. The example is shown in thevolley in fig. 6 : A marked increase of frequency of discharges is to be seen in the second and third volleys shown in fig. 6, B, accompanying the increase of depth of breathing. The discharges are to be seen also in the silent periods, although their frequency is rather smaller. After a while the silent periods appear again, and the course of impulse discharges becomes regular, the frequency of impulses being a little larger than in the normal volley (fig. 6, C).

The larger amount of the chemical produces at first the inhibition of the discharges : the neuron discharges continuously with frequency which is far smaller than that of the normal volleys, showing rapid periodical change of frequency of impulses. The frequency of the discharges is gradually increased in a course of time, and the discharges have a tendency of

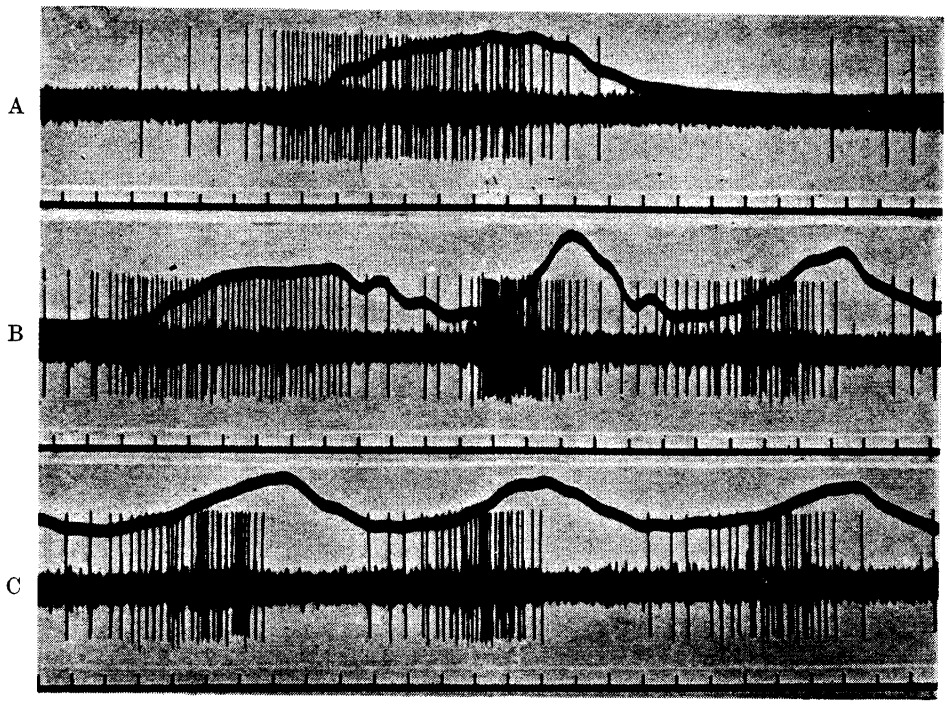

Fig. 6. Effects of aminocordine upon the discharges of a single inspiratory neuron.
Cat (2.5 kg.) decerebrated. 0.1 cc. of 25% aminocordine (10 mg/kg) is intravenously administered. A. Normal volley. B. 8 seconds, C. 14 seconds after administration of the chemical. Time marks 1/12 sec..

grouping until they form the volleys, the rhythm of which is larger than that of the normal volley. These final results are similar to those produced by the administration of a smaller amount of the chemical. From the results described above we have reason to believe that, although the chemical acts essentially extcitatorily (directly and indirectly for the respiratory centers), a larger amount of chemical acts as too strong a stimulus for centers and causes the exhaustion of the centers, thus producing apparent inhibitory effects. We have recently reported that similar results are also able to be obtained by a strong inflation of the lung[9].

The effects of lobeline upon the discharges of the inspiratory neuron :— When 0.5 cc. of 1% lobeline is intravenously administered, the discharges are at first completely abolished. This inhibitory effect is only transitory (about 2 seconds) and soon

followed by excitatory effects, that is, the shortening of the duration of the volleys, as well as of silent periods, and the increase of frequency of impulses. The example is shown in fig. 7.

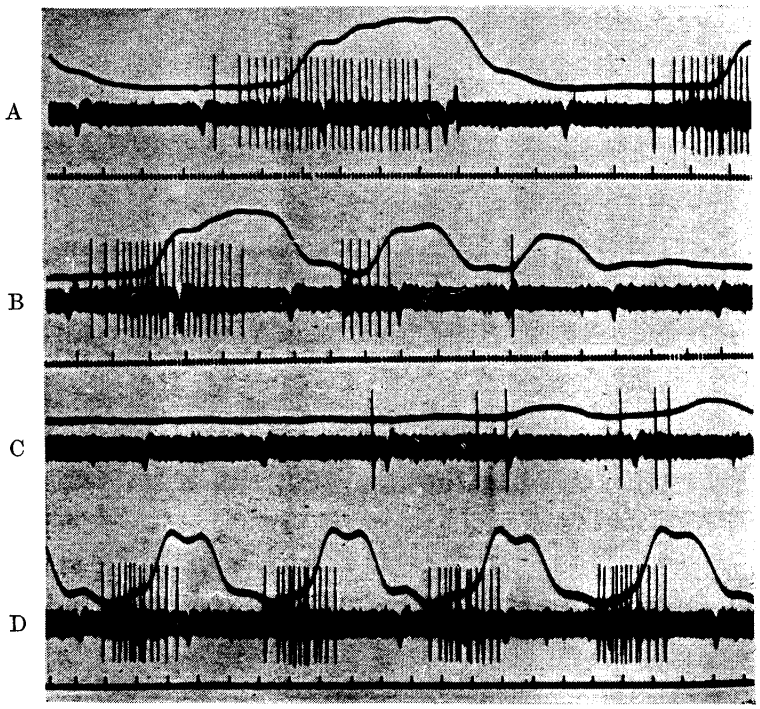

Fig. 7. Effects of lobeline upon the discharges of a single inspiratory neuron.
Cat (3.5 kg.) decerebrated. Both caretid arteries ligatured. 0.5 cc. of 1% lobeline (1.4 mg/kg.) is administered into the saphenous vein. A. Normal volley. B. 8 seconds, C 10 seconds and D. 15 seconds after administration of chemical. In B and C an inhibitory effect can be observed while in D an excitatory effect occurs.

The effects of morphine upon the discharges of the inspiratory neuron :— A small or moderate amount of morphine (7—10mg. per kg. body weight) produces a prolongation of the volleys, as well as of the silent periods, while the frequency of impulses show sa characteristic change. In the most usual pattern, i. e.. the trapezoidal pattern[8], the rate of crescence of frequency is considerably slowed down (fig. 8, B and C). In the stage of constant frequency the frequency of impulses increases gradually

(fig. 8, B), until it becomes larger than normal (fig. 8, C). This increase of frequency is, however, maintained only transitorily and sooner or later gives place to its decrease, accompanied by a considerable decrease of the number of impulses.

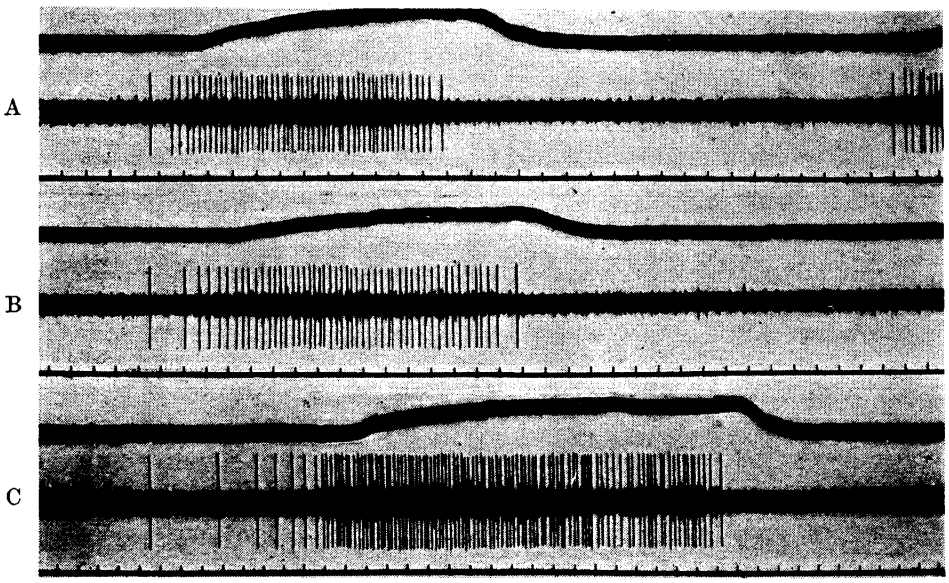

Fig. 8. Effects of morphine upon the discharges of a single inspiratory neuron. Cat (3.5 kg.) decerebrated. 2.5 cc. of 1% morphine (7mg/kg) administered intravenously. A. Normal volley. B. 15 second and C. 60 seconds after administration of chemical. In C 1.0 cc. of morphine administered additionally.

On the whole it can be said that the change of frequency of impulses shows on the one hand the sign of inhibition and on the other hand that of excitation.

The larger amount of morphine (20 mg. per kg. body weight) produces the excitatory effect no more and exclusively the inhibitory. In this case the silent period is prolonged, the frequency of impulses decreases considerably, and the stage of constant frequency is shortened, while that of decrescent frequency is so remarkably prolonged that the whole duration of the volley is not shortened but rather prolonged. Fig. 9 shows an example. The pattern of discharges differs from that shown in fig. 8 and belongs to pattern D, in which the stage of crescent frequency is lacking (see our previous report[8]). The more the narcosis is deepened, the longer the interval of successively discharging impulses becomes. After a while the duration of the volley is

successively shortened from one volley to another until at last the discharge is abolished suddenly.

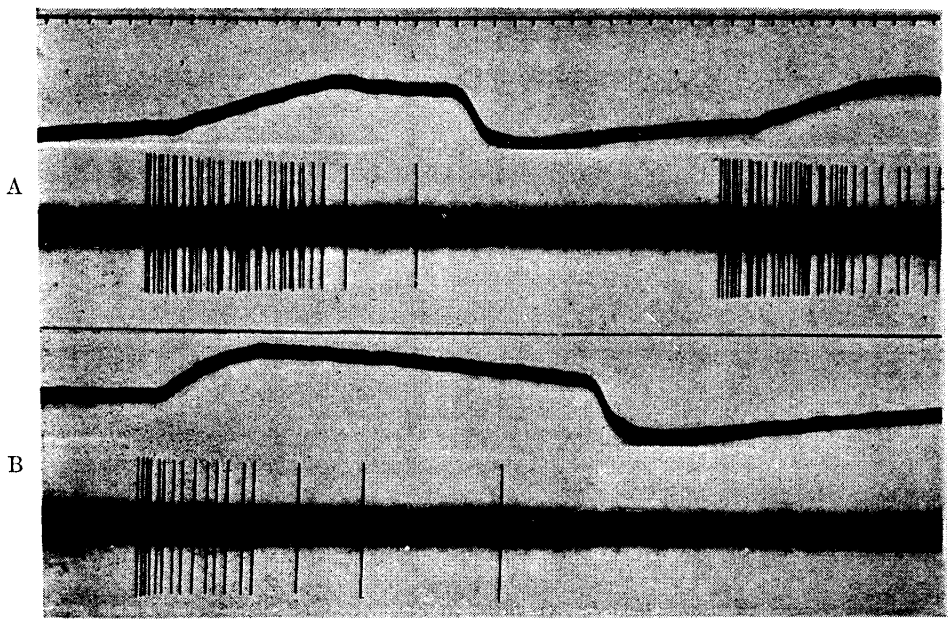

Fig. 9. Effects of morphine upon the discharges of a single inspiratory neuron. Cat (2.5 kg.) decerebrated. 5 cc. of 1% morphine is administered into saphenous vein. A. Normal volley. B. 15 seconds after administration of chemical.

Discussions

From the results described above, the following phenomena can be enumerated as the sign of raised activity of the centers, that is, a) a remarkable increase of frequency of impulses in the stage of constant frequency of the volley, b) a rapid increase of frequency of impulses in the stage of crescent frequency of the volley and c) a shortening of the duration of the volleys, as well as of silent periods, although the prolongation of the former may sometimes occur. We believe that the most essential sign of raised activity of the centers is the increase of frequency of impulses, while the change of duration of volleys and of silent periods may be phenomena produced secondarily, which are particularly due to the vagus-respiratory reflex, as *Scott*[14] presented in evidence.

The phenomenon described in b) is reflected in increase of

the rate of flow of air in the lungs or in rapid increase of contraction velocity of inspiratory muscle. The phenomenon described in c) is reflected in acceleration of the rhythm of breathing. The phenomena described in a) and c) are related to the depth of breathing. When the activity of the centers is raised above normal, the breathing may sometimes be deeper and sometimes shallower than normal, owing to the combinations of the two factors described in a) and c), and consequently the minute respiratory volume may be rather diminished below the normal level, in spite of the raised activity of the centers.

As the sign of the depressed activity of the centers, one can enumerate the phenomena which are exactly opposite to those of the raised activity of the centers, and the most essential sign is the decrease of impulse frequency which is especially clearly observed in narcosis by a moderate dose of morphine, as well as in the recovery stage from apnea. When the centers are moderately inhibited, the smaller frequency of impulses is often accompanied by the prolongation of the volleys, which is especially clearly observed in the recovery stage from apnea. In such cases from the measurement of the amplitude of a mechanogram, one can not thus decide whether the centers are in the raised state of activity or not. From this point of view the increase of depth of the breathing observed in an animal with vagi cut[9], is not perceived as a sign of the raised activity of the respiratory centers, because the frequency of impulses is in that case lower than that of the normal.

Summary

In decerebrated cats the impulse discharges were detected by means of an unipolar microelectrode from a single inspiratory neuron in the respiratory centers, and the change in discharge produced by administration of stimulating, as well as depressant agents, was studied. The results were summarized as follows.

1) Inhalation of the air containing an excess of carbon dioxide, as well as the air deficient of oxygen and the intravenous administration of a small dose of caffeine, aminocordine and lobeline produced a) a remarkable increase of frequency of

impulses in the stage of constant frequency of the volley, b) a rapid increase of frequency of impulses in the stage of crescent frequency of the volley and c) a shortening of the duration of the volleys, as well as of silent periods.

2) In narcosis by a moderate dose of morphine, as well as in the recovery stage from apnea produced by over-ventilation, there were observed the phenomena which were exactly opposite to those described in 1).

3) It was concluded that a most essential sign by which one can discern whether the activity of the respiratory centers is raised or depressed, is the changes of the frequency of impulses produced from an inspiratory neuron.

The expense of this research was defrayed from the grant in aid of the Ministry of Education.

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