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Respiratory Arrest Induced by Unilateral Lesion(s) of the Medullary Inspiratory Center in Cats[1] (38008)

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The medullary inspiratory center has been localized in cats by electrical stimulation (1, 2) and microelectrode recording (3–6). General consensus is that it is located in the lateral and ventral reticular formation on both sides of the midline. In this study, electrolytic lesions were made in the medullary inspiratory center and the effect on respiration observed.

Materials and Methods. Sixty-five cats of either sex, weighing 2.5–3.6 kg, were anesthetized with sodium pentobarbital, 35 mg/kg ip. The trachea was cannulated and connected to a pneumotachograph which allowed recording of respiratory frequency and air flow via a volumetric low pressure transducer (Grass Instrument Co., Model PT5A) and Grass polygraph. Arterial blood pressure was recorded from the left femoral artery using a Statham P23AC strain gauge transducer. Cannulation of the femoral vein allowed administration of 0.9% sodium chloride solution in cases of excessive bleeding during craniotomy. In case of excessive bleeding (4 out of 65 cats), an additional dose of the anesthetic, 5 mg/kg iv, was given after the animals had received 0.9% saline solution to replace the blood loss.

Following cannulation of the femoral vein, the animal was fixed in a stereotaxic instrument (David Kopf, Tujunga, California). Occipital craniotomy was performed in order to expose the medulla oblongata and the cerebellum.

In localizing the inspiratory center of the medulla, the respiratory response to electrical stimulation of the medulla was employed. Areas where electrical stimulation elicited deep sustained inspiration were considered parts of the inspiratory center. Stimulation was delivered through one unipolar stainless steel electrode, which was 0.5 mm in diameter, insulated except for a bare tip of 0.5 mm length, inserted into the medulla stereotaxically at an angle of 25° from the vertical plane directing downward and forward. The indifferent electrode was attached to the ear bar of the stereotaxic instrument. The stimulating current consisted of square wave pulses with the following characteristic: intensity, 1–2 V; frequency, 50–100 Hz/sec; pulse duration, 0.5 msec.

Having localized the areas where electrical stimulation brought about deep sustained inspiration, electrolytic lesions were placed in them. Each cat was given either one unilateral lesion, one midline lesion, or bilateral lesions placed symmetrically about the midline.

Lesions were produced by applying 5, 10, 20, 30, or 40 mA direct current for 20 sec through the stimulating electrode from an electrolytic lesion maker (Stoelting Co., Chicago, IL).

There were eight different combinations of location and severity of lesion and these were separated into the groups shown in Table I.

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TABLE I. Tabular Presentation of the Cat Groups According to the Place of the Lesion and Strength of the Lesioning Current.

Group	Number of cats	Lesion	Applied current (mA)
I	5	unilateral	5
II	5	bilateral	5
III	5	midline	5
IV	10	unilateral	10
V	10	midline	10
VI	10	midline	20
VII	10	midline	30
VIII	10	midline	40

Upon completion of the experiment, the animal was killed with a lethal dose of sodium pentobarbital, and the brain was perfused with physiologic saline, followed by 10% formalin. Then, the brain was removed and placed in 10% formalin for 48 hr. After this period, that portion of the medulla which is rostral to the obex was serially sectioned and the 10-μm-thick sections were stained with hematoxylin and eosin. The stained sections were microscopically examined for the electrode pathway and the site and size of the lesions ascertained.

Results. Stimulation of the regions of the medulla described below evoked deep sustained inspiration for the duration of the electrical stimulation. Based upon the response to electrical stimulation, the inspiratory center was localized from 1 mm caudal to 3.5 mm rostral to the obex, between midline and 3.5 mm laterally on both sides, and commencing 2 mm below the dorsal surface of the medulla to 1 mm posterior to the ventral surface (Fig. 1). These anatomical boundaries are consistent with those reported by other investigators in cats (1, 2).

Following unilateral 5-mA lesions (Group I), rhythmic breathing commenced with slightly diminished air flow and respiratory

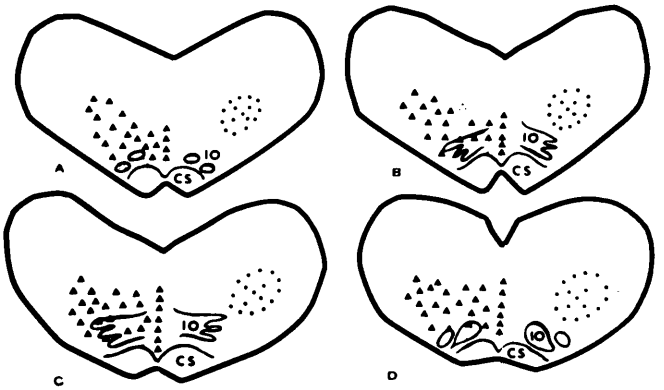

FIG. 1. Composite cross-sectional diagram of the medulla oblongata. The plane of the section is 25° from vertical, tilting forward and downward. The sections are 1 mm apart. Section A is 3 mm rostral to obex and Section D is at the level of obex. The solid triangles are areas where electrical stimulation produces maximal sustained inspiration. The open triangles are areas where electrical stimulation produces submaximal inspiration or increased respiratory frequency. The dots on the right represent the area where a lesion, made by 10-mA direct current, causes cessation of breathing. This area and that of the inspiratory activity are present on both sides, but for the sake of clarity, each one is shown on only one side. CS, corticospinal tract; IO, inferior olive.

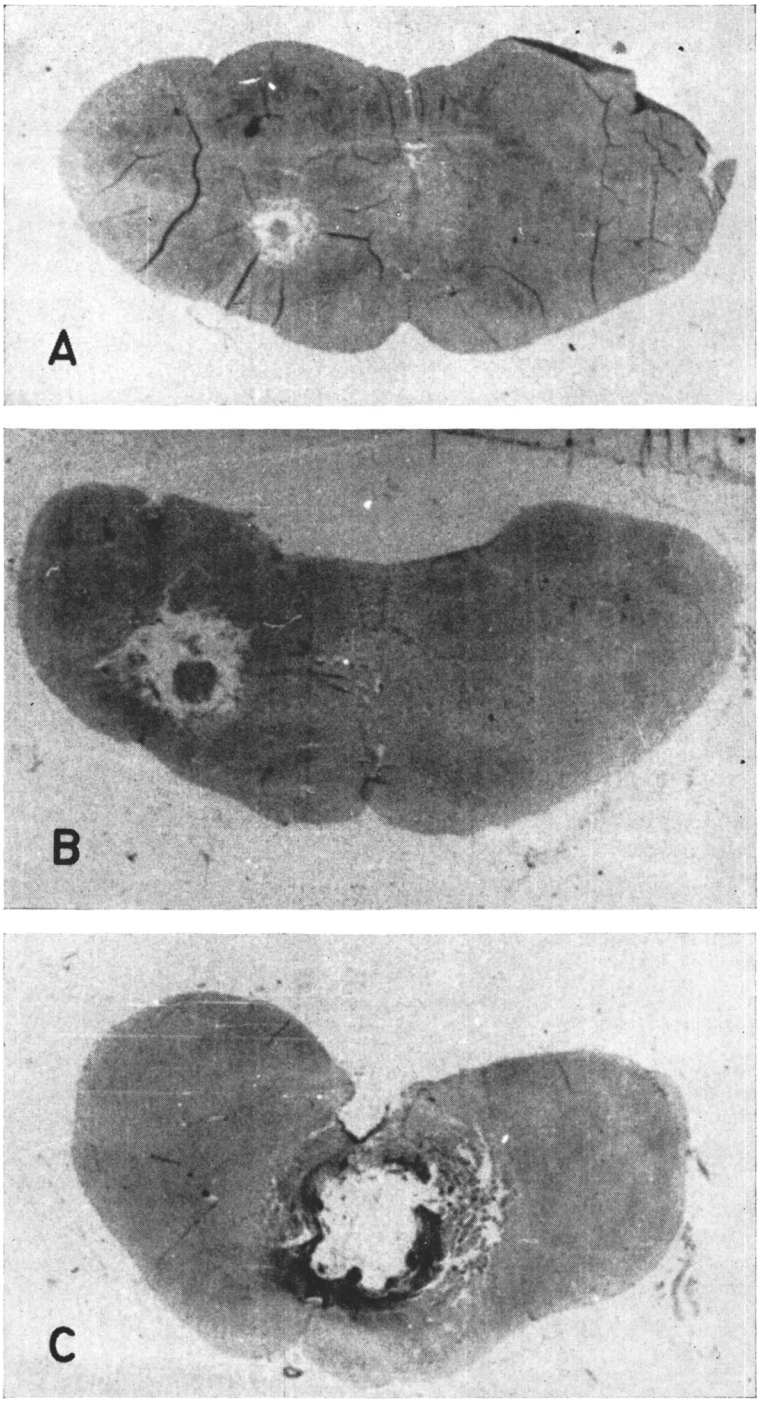

FIG. 2. Photomicrographs of the cross sections of the medulla oblongatas, showing lesions produced by electrolytic currents. In A, the left side lesion was made by 5 mA dc applied for 20 sec (group I). In B, the left-side lesion was made by 10 mA dc applied for 20 sec (group IV). In C, the midline lesion was produced by 40 mA, applied for 5 sec (group VIII). Hematoxylin and eosin stain. ×10.5

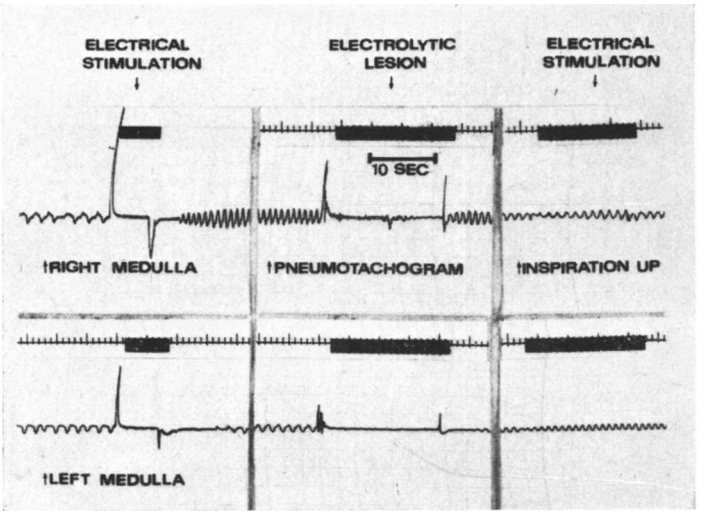

FIG. 3. Respiratory response to electrical stimulation of the medullary neurons before (left strip) and after (right strip) producing electrolytic lesion (middle strip) in a cat of group III. Lesion was placed in both right (upper tracings) and left (lower tracings) medulla. The lesion in the right side was placed before the stimulation and lesioning of the left side. Each lesion was produced by 5-mA dc applied for 20 sec. Notice that respiration continues in spite of bilateral lesions (lower-right-hand panel).

rate. Figure 2A is a photomicrograph of the medulla displaying the unilateral lesion made by 5 mA direct current.

Likewise after bilateral 5-mA lesions (Group II), breathing started with reduced frequency and air flow (Fig. 3).

The unilateral 10-mA lesions (group IV) caused cessation of respiration (Fig. 4). After respiratory arrest, there was an initial rise in the arterial blood pressure, followed by gradual diminution. But the primary failure was that of respiration rather than circulation, because artificial respiration invariably restored heart beat and blood pressure to normal, but as artificial respiration was discontinued, circulatory failure gradually ensued. Figure 2B is a photomicrograph of the medulla depicting the unilateral lesion produced by 10 mA direct current.

During the induction of midline lesions by 5 (group III), 10 (group V), 20 (group VI), and 30 mA (group VII), respiration ceased, but was reestablished at the termination of the lesioning current. Diminution of the air flow and respiratory frequency was observed relative to the strength of the current used. Midline lesions created by 40 mA (group VIII) caused death due to respiratory failure. Figure 2C is a section of the medulla showing the midline lesion produced by 40 mA direct current.

In general, histological studies revealed that the lesion size was proportional to the current intensity, i.e., the greater the current intensity, the larger the lesion size.

The arterial blood pressure often rose sharply while making the electrolytic lesions, although the response to electrical stimulation of the same area was a depressor one (Fig. 4). The pressure gradually returned to the baseline level following termination of the electrolytic current.

Discussion. The results presented above indicate that all the medullary inspiratory neurons are not necessary for normal breathing, i.e., rhythmic respiration without inspiratory or expiratory pause (7), at least in cats. Lesions produced by 5 mA direct current (groups I, II, III), even when placed bilaterally, did not cause cessation of respiration. However, the fact that the rate of breathing and air flow diminished indicates that normal respiration is controlled by the activity of numerous medullary inspiratory neurons.

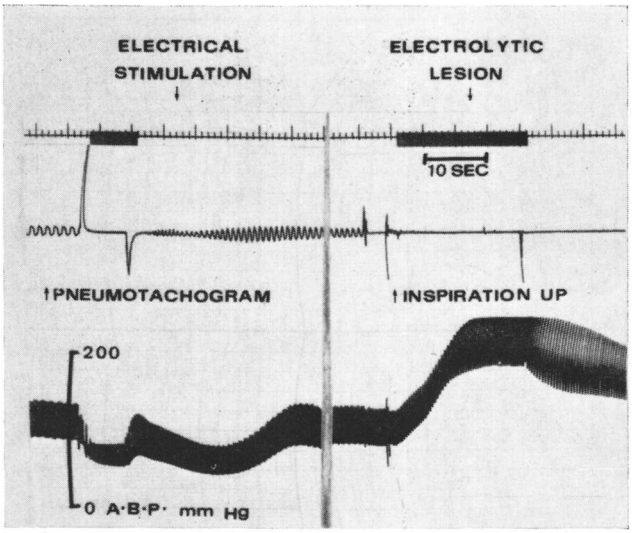

FIG. 4. Cessation of respiration due to unilateral lesion in medullary inspiratory center produced by 10-mA dc applied for 20 sec. The left strip shows recordings during stimulation and the right strip during lesioning. The upper tracing is the time record superimposed with stimulation and lesioning signals, the middle tracing is respiration, and the lower tracing is arterial blood pressure (A.B.P.). Note the sharp elevation of arterial blood pressure during lesioning although the pressure dropped on stimulation. The tracings belong to a cat in group IV.

Cessation of respiration by a large enough lesion on one side, produced by 10 mA direct current (group IV), points to the vital role played by each side of the medulla for continuation of respiration. Although not all the lateral inspiratory neurons were destroyed by such a unilateral lesion, as evidenced by inspiratory response to electrical stimulation at a point 2–3 mm away from the center of the 10-mA lesions, apparently the remaining inspiratory neurons of the ipsilateral side were not sufficient to maintain the essential role that each side seemingly has as far as continuation of respiration is concerned.

The midline region apparently is not as crucial as the lateral region. This statement is supported by the observation that only large lesions produced by 40 mA (group VIII) caused respiratory arrest.

The area which was localized as the medullary inspiratory center corresponds with the region outlined by Pitts, Magoun, and Ranson (1) and Tabatabai (2) in cats, by Beaton and Magoun (8) in monkeys, and by Amoroso, Bell, and Rosenberg (9) in sheep. Maximal sustained inspiration was the common response to electrical stimulation of the midline region. But Haber *et al.* (3) and a number of other investigators (4–6) failed to find midline inspiratory neurons while making microelectrode recordings from the medullary neurons. Although the presence of midline inspiratory neurons cannot be ruled out, the results of the midline lesions shown may be interpreted to mean that there are not nearly as many inspiratory neurons in the midline as in the lateral region, since it took large midline lesions to bring about respiratory arrest (group VIII). On the other hand, if there are indeed no midline inspiratory neurons, it can be assumed that the axons of the inspiratory nerve cells converge toward the midline where electrical stimulation causes maximal inspiration and lesion induces respiratory arrest. Figure 5 shows the lateral inspiratory region where one unilateral lesion made by 10-mA current caused cessation of respiration. This region fits well within the boundaries delineated by microelectrode recording of Haber *et al.* (3)

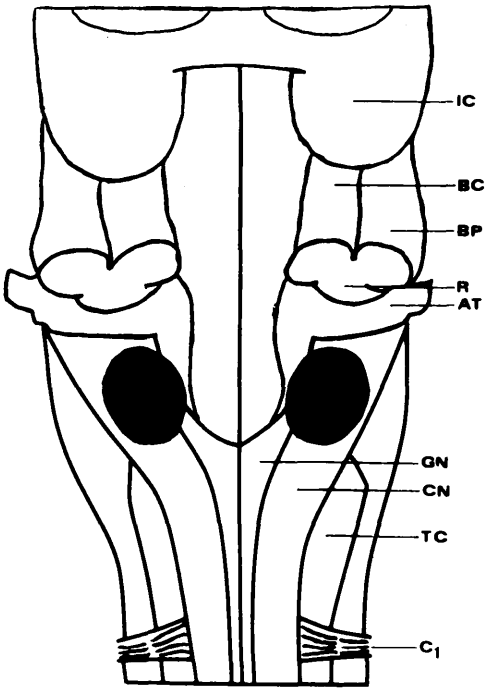

FIG. 5. Schematic presentation of the dorsal brainstem of the cat. The two black ovoids represent areas where electrical stimulation causes maximal sustained inspiration and whose lesion, either on the right or on the left, made by 10-mA dc applied for 20 sec results in respiratory standstill and death. The abbreviations are as follows: AT, acoustic tubercle; BC, brachum conjunctivum; BP, brachium pontis; C_1, first cervical spinal nerve; CN, cuneatus nucleus; GN, gracilis nucleus; IC, inferior colliculus; R, restiform body; TC, tuber cinereum.

and other investigators (4–6) as the region of the medullary inspiratory neurons.

Summary. Effect of electrolytic lesions of the medullary inspiratory center on respiration was studied in 65 sodium pentobarbital-anesthetized cats. The current was applied through a stainless steel electrode inserted stereotaxically into the medulla. Unilateral or bilateral lesions produced by 5 mA applied for 20 sec induced no respiratory arrest. Unilateral lesions produced by 10 mA applied for 20 sec evoked terminal apnea. Midline lesions made by 5, 10, 20, and 30 mA each applied for 20 sec failed to cause respiratory arrest. However, those midline lesions produced by 40 mA stopped breathing. These results show that the inspiratory neurons of each half of the medulla are crucial for the maintenance of respiration. Further, they confirm that most of the medullary inspiratory neurons are in the lateral reticular formation.

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