ON THE RESPIRATORY CENTRE

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Received for publication January 17, 1936

Lumsden (1923) suggested that the respiratory centre was divisible into three or four parts; only the most caudal of his centres, the gasping centre, lay below the striae acusticae. The work of numerous observers has shown that Lumsden's work is inaccurate,—Schoen (1929), Teregulow (1929), Henderson and Sweet (1929); and Henderson and Sweet particularly, have shown that respiration, normal in type, occurs in cats even if complete transverse sections are made below the striae acusticae. Such respirations are usually slower than normal, but adequate. It is of course clear that the medullary respiratory centre is, or may be, influenced in its activity by fibres reaching it from higher levels.

Since the work of Henderson and Sweet, the authors of this paper have been engaged intermittently in attempting to delimit the respiratory centre or centres and trace the afferent and efferent connections. All experiments have been made in cats and in all cases the animals have been young, incompletely developed animals and from 1.5 to 2 kgm. in weight. Operations have been carried out under urethane and ether. Before making incisions a clear view of the area of the medulla involved was obtained, either by the complete ablation of the cerebellum, using the method described by Henderson and Sweet, or more usually by removing the central portion of the occipital bone with a rongeur and the central portion of the cerebellum with a scoop. All bleeding was arrested. Sections were made with small splinters of safety-razor blades, using a gentle sawing motion. After the conclusion of the experiment the head of the animal was placed in formalin, and only after thorough fixation was the area involved removed. If the gross examination warranted it, the material was cut in serial sections, usually transverse, stained and mounted in series and examined by E. H. C.

In the serial sections, transverse lesions were often hard to delimit. The lesion rarely lay in the plane of the sections; if there was diffusion of blood this often occurred in another plane than that of the lesion and obscured the lesion proper. Further, such a fine incision, if not accompanied by bleeding, often produced such slight changes that only careful scrutiny could trace its course and extent. Indeed, in some cases this proved impossible.
A complete series of 30\(\mu\) sections through a normal medulla was prepared and from this a plan of the various important structures was made. In making the plan, 10 per cent was allowed for shrinkage. Owing to the great kindness of Prof. J. W. Papez (1929) who published several sections through the medulla of the cat in his book, we have been provided with the serial numbers of the sections published, and also the thickness of the sections cut by him. Using these data, we have been enabled to check our plan against his figures. The plan thus prepared forms the basis for

Fig. 1. Plan to scale of the medullary area prepared as described in the text, showing the relative positions of the important structures referred to in the text, and also the levels of the sections published by Papez.

figure 1. Further, as in the reproduction of photographs of the lesions in our preparations, much detail would not appear, it seemed advisable to plot these lesions on photographic reproductions of Papez' figures when possible, since this would enable any person interested to compare our figures directly with Papez' published ones, and hence obtain the relation of our lesions to other structures. This procedure also enabled us to present our results with the use of fewer figures.

Typical and selected experiments only have been described and assigned arbitrary letters for convenience of reference.
We would like to support the conclusions drawn by Porter, namely, that the cutting of nerve tracts does not necessarily produce an inhibition of the cells from which they arise or to which they run. Usually a lesion caused either no effect or a very temporary one, but in some cases respiration failed gradually during a few breaths. In these cases the failure was probably due to the effect of an attendant hemorrhage or interference with blood supply and was very obviously so produced in certain cases. In most such cases more or less prolonged artificial respiration leads to a recovery of function. If the lesion mechanically damages respiratory cells, they of course may not recover, and it is always difficult to estimate what tissues have thus been injured, but certainly cells which lie within 200 micra often function normally and cells lying even closer may retain their function.

The method has however certain disadvantages; that of identifying the lesions is one. The more important is that the lack of function may be due to the pressure produced by the diffusion of blood. The third lies in the great difficulty in exactly repeating any experiment. Nevertheless, this method has been almost exclusively employed, as it was found experimentally that electrical stimulation might give equivalent results from widely separated points, probably owing to stimulation of fibre tracts. The thermocautery has been used; again it appeared almost impossible to produce lesions comparable in position and depth, and ample evidence was acquired that temporary depression was due to the heat reaching cells beyond the area destroyed, and of course such damage may be invisible.

Henderson and Sweet found that respiration of a normal character persisted after a transverse section below the striae acusticae. Complete transverse lesions cut the descending vasomotor pathways and entailed a severe fall in blood pressure, but sections involving the medial third of the medulla, as was reported by Sweet and Henderson, do not have these defects. In their experiment, no. 12, plan 1, a dorso-ventral lesion which was limited laterally by the central portion of the nucleus ambiguus and the uncinate fasciculus and lay at a level a little caudal to Paper's section 135, i.e., cephalad to the hypoglossal nucleus and about at the junction of the upper and middle quarters of the inferior olive, left respiration intact and normal in character.

This work shows then that the respiratory centre lies below the striae acusticae and probably lower than the cephalic extremity of the hypoglossal nucleus.

Two possible sites have been suggested for the respiratory centres in this area. The first, that of von Bechterew (1908), who suggests that it lies in the reticular formation about the level of the hypoglossal nucleus; and the second that of Ramón y Cajal (1909), that it lies in the commis-
The a priori reasons for the latter suggestion are obvious. Vagus afferents play an important part in respiratory control. These fibres enter the nucleus of the tractus solitarius and at the same or at a lower level synapse with its cells, from which fibres pass to the respiratory centre. Now the two nuclei of the tractus solitarius unite across the mid-line below the obex, forming the commissural nucleus, whose area is shown in plan 1, figure 1. From the lower parts of this nucleus, the solitary tracts again diverge and could form the paths of efferent respiratory impulses. The validity of this hypothesis was tested by clipping away with scissors or cutting away with the knife, the whole of this nucleus. Cat a was the most successful of these experiments, as no portion of the commissural nucleus was found histologically. The removal was completed at 11:10 a.m. and respirations became small and inadequate. Artificial respiration was given till 1:29, when the respirations were smaller than normal at about twice the normal rate and showing slight irregularities of a gasp-like character. Respiration, however, improved and at 2 p.m. it was more regular but still fast. Blood pressure had been low throughout this period and was at this time only 35 mm. Hg. An intravenous injection of 0.1 mgm. adrenaline caused some reflex slowing and decrease in depth, and respiration was somewhat more irregular. In other cases only an isolated group of some 100 cells was left. All these cases showed more or less lasting respiratory depression as a result of the operation. In cat a the area cut away is shown in plan 1, and the depth of the lesion is indicated at two levels in sections 129 and 130 in figure 2. As will be seen in section 130, the lesion reaches nearly to the level of the hypoglossal nucleus and did so over practically the lower half of this nucleus. There was a prolonged depression of respiration and no doubt some damage was done to some respiratory cells. These experiments, then, lend support to the suggestion of von Boeckhew that the respiratory centre lies in the reticular substance, ventral to the xii nucleus, and demonstrate completely that the respiratory cells do not lie in the commissural nucleus.

As a means of delimiting the respiratory area, we resorted to longitudinal and transverse sections. We felt ourselves justified in considering that the respiratory centres lie in the medial portion of the medulla, as longitudinal sections lateral to this region did not abolish respiration. For example, in cat e, a longitudinal cut was made, whose position is shown in plan 2 and sections 131, 130 and 129. Respirations became somewhat apneustic in type for a few minutes and then slower than normal and ample, apparently normal in type as both sides of chest and diaphragm participated in the movements. The cut at the level of Papez 131 lies just medial to the solitary tract at its dorsal end and is also medial to it in 130.

In experiment f the cord was split in the midline over segments 3–6.
(At postmortem it was found that in segments 3–4 the lesion was very slightly to the left of the midline; in the others, however, in the midplane.) A longitudinal incision on the right side was then made from a point about 2 mm. cephalad to the obex and lateral to the xii nucleus. The lesion extended ventrally to the inferior olivary sac (plan 2, sections 131 and 130). Caudad the lesion did not penetrate so deeply, being only to the level of the xii nucleus and approaching the midline, so as to lie just medial to this nucleus. Almost the whole of this section was made without any apparent change in respiration, save a slight decrease in depth (respiration was recorded quantitatively) but a slight extension cephalad and the insertion of a small probe led to a definite decrease in depth and rate. Consequently artificial ventilation was employed for 20 minutes, respirations being then slow and weak. On opening the abdomen only the left diaphragm appeared active. The diaphragm was then split in the midline and the left half still moved and the right did not. The production of this lesion had apparently damaged a part of the respiratory mechanism.

From these and similar experiments the conclusion has been drawn that the respiratory cells lie in the medial third of the medulla.

Fig. 2. Sections 131, 130, 129 are reproductions of the figures with corresponding numbers in Papez’ book. The position of the lesions at the respective levels is shown. All the structures dorsal to the curved lines for cats d, c and a were either removed or destroyed. The striae on lines for cats d and c indicate the areas showing histological change due to heat.
In view of the conviction that the respiratory cells lay in the medial third of the medulla, transverse sections were made, involving the medial third only, with the purpose of defining the cephalad extent of the area containing the respiratory cells. The caudal limit must be set by the pyramidal crossing which begins only about one millimetre below the obex in cats of the size used.

In cat g, the lesion (plan 2) extended on the left through the fasciculus solitarius and on the right to just beyond the lateral margin of the xii nucleus. The width and level are shown in plan 2. Ventrally it extended on the left nearly to the inferior olive but on the right not so deeply. The transverse cut seemed to be about 2.3 mm. cephalad to the caudal end of the inferior olive or about 1.8 mm. cephalad to the obex at the junction of the upper and middle thirds of the xii nucleus. It lies between Papez' figures 131 and 134. In spite of a good deal of bleeding and definite diffusion of blood as seen in the sections, which led to inadequate respiration and the need of artificial ventilation for a time, the respirations became normal in rate and depth (recorded quantitatively). On being bled, gasps appeared, intermingled with normal respirations. Neck and shoulder muscles were involved.

In cat h, a transverse incision (level and width shown in plan 2) was made reaching lateral to the fasciculus solitarius on the left, and somewhat further on the right, and ventrally to the upper surface of the inferior olive on the left but not quite so deep on the right and lying about 1.4 mm. cephalad to the obex or about the junction of the upper and middle thirds of the xii nucleus. There was a good deal of suffusion of blood below and above the level of the section, and owing to a defect in the normal closure of the spinal canal which persisted as a split, the exact level was hard to identify, and hence the hatching below the line in plan 2 is intended to represent the area in the centre of the plan in which the lesion proper occurred. Respiration continued after the cut was made for a few breaths, which were about half normal depth and at half the rate and then failed. After 10 minutes artificial ventilation the cat breathed for two minutes, but inadequately. After a further hour's ventilation, the blood pressure was good and respiration was more regular and slow, but inadequate in depth. Another two hours' ventilation did not lead to any improvement; blood pressure was low. When gasps supervened, there were no movements of the neck or shoulder muscles. It seems very probable that this lesion had cut into the respiratory area, or that blood diffusion had damaged certain of the respiratory cells. The failure of gasping movements of the neck and shoulder muscles, which has also been observed in other cases with low sections, even when gasp-like movements were made by the abdominal muscles, suggests that the innervation of certain of the accessory muscles arises from a higher level than that of the abdominal.

It would seem then that the respiratory cells are included in the medial
third of the medulla posterior to a level some 2 mm. cephalad to the obex in cats of this size, i.e., from a level more cephalad than the junction of the upper and middle thirds of the xii nucleus and extending to or below the obex.

Further evidence that the respiratory cells lie towards the midline may be drawn from a long series of experiments in which longitudinal incisions were made in the midline. Langendorff (1881) has frequently been quoted as saying that a midline incision through the medulla did not interfere with normal respiration, save that under other experimental procedures some evidence of independent action of the muscles of the two sides might occur. However, on looking up his work it is evident that his incisions were made from the obex cephalad. We have had the same experience, for instance, in cat 1 where an incision cephalad was followed by normal, though perhaps not so deep respiration, while when the cut was prolonged caudad for 1 mm., respiration ceased and even prolonged ventilation did not lead to its recovery. In other experiments incisions below the obex did not lead to failure, while when prolonged above it, failure was prompt, complete and permanent. At least a dozen experiments of this type were carried out.

There are two possible explanations for these observations: a, that the respiratory cells lie so close to the medial plane that the section produced sufficient mechanical damage as to cause arrest of their function; or b, that efferent fibres from the respiratory cells cross like those from the red nucleus before descending the cord. This latter suggestion is contrary to the evidence presented by Gad and Marinescu (1893) who burnt away areas of the medulla by means of small hot drops of glass. Unfortunately, they give no description of the extent or exact position of these lesions. Respiration ceased on the side of the lesion. This is of course possible if the lesion cut the respiratory path after crossing. We attempted to imitate these experiments by using a fine thermocautery. In two cases a distinct unilateral failure of respiration occurred, but on the opposite and not on the same side. The areas involved by these lesions are shown in plan 3 and in sections 131 and 130, lesions c and d.

Many of the experiments were indefinite. Further, there is evidence in the experiments of Porter (1894), Rothmann (1902) and other workers that a partial crossing, at all events, occurs at the level of the anterior horn cells. A section in the cervical cord may lead to the diaphragm moving normally or to failure on the same side. If, however, the opposite phrenic is cut, movement will begin in the apparently paralysed side. It may fairly be concluded from the experiments of these workers that the crossing at the anterior horn cell level in the cord is not dominant under normal conditions but in cases of a unilateral lesion may be adequate to produce an approximately normal diaphragmatic movement. Conse-
quently, clear cut results could only be obtained with certainty if the spinal cord were split in the midline so as to prevent crossing at the anterior horn level. Yet when this procedure has not been carried out, a failure only on one side requires consideration, as the presence of an anesthetic and of the operative procedures may lead to the respiratory impulses not crossing at the anterior horn cell level so as to produce respiration on the opposite side. This frequently occurred in the experiments carried out by the authors cited, and in our own cases mentioned below with cord lesions. While splitting the cord alone has no apparent effect on respiration, the operative interference does not leave the animal in as good a state as if it had not been performed. These experiments have not led to a positive conclusion as to whether a medullary crossing occurs or not. Further, it is always possible that a lesion such as that in cat f, quoted above, might have affected the fibres after they had crossed.

As the course of the descending efferent fibres from the respiratory centre to the anterior horn cells is not generally recognized in textbooks of physiology, we repeated some of the experiments done by Gad and Marinescu, Porter, and Rothmann, with a somewhat varying technique. The recorded experiments of Rothmann and Porter were made on dogs and rabbits. Gad does not state the animal used. According to these authors, the descending efferent fibres lie adjacent to the anterior horn. Our experiments were of the following type. After baring the lower medulla and upper segments of the cord dorsally, a small section of the bodies of the 2nd and 3rd cervical vertebrae was removed and a section of the ventral white matter was made; this indeed often invaded the grey matter as in figure 3. No change in respiration was seen. A longitudinal section was then made in the cord so as to cut the pyramidal crossing; in only one case was this quite complete, but in others only a few of the lower fibres were uncut. This, too, did not affect respiration. Sections were made then in the dorsal and lateral area of one side at slightly different levels in the second and third segments of the cord. Section of areas such as that between I and the surface (fig. 3) or II or b and the surface have no effect, but a section between III and the surface (all these were made in the same animal and though at slightly different levels have been indicated on the same diagram) or between a and the ventral surface cause respiration to cease on the side of the lesion. The other side moves...
amply and often, and adequate ventilation is obtained. If such an animal were bled somewhat, as in cat j, gasps appeared and these too appeared to be unilateral only. On section of the diaphragm in the midline only one side moved, either in respiration or in gasps. In cat k, 0.5 mgm. of nicotine had been given intravenously shortly before the section of the cord in the ventral area. Ipsilateral respiration ceased, on bleeding gasping occurred, the gasps involving only the heterolateral muscles of shoulder and neck as well as the diaphragm, in spite of the fact that twitches were occurring irregularly in the neck muscles of both sides, due to the nicotine. On splitting the diaphragm, only the heterolateral half moved, even in the gasps. While we do not deny that in the cat some crossing of descending fibres from the respiratory centre may occur, as Porter has so clearly shown in the dog, under the conditions of our experiments possibly due to the urethane used, they were not evident and the descending respiratory impulses appeared only to innervate anterior horn cells of the same side. Under the conditions of our experiments we saw no evidence of independent coordinated spinal respiration, even when the conditions were most favourable.

We also attempted to delimit the course of the fibres from nucleus of the tractus solitarius to the respiratory cells. These might leave the nucleus at the level at which the vagus afferents entered the nucleus and pass medially and caudally towards the respiratory centres. However, stimulation of the vagus after making one of the incisions across the medial third of the medulla, showed that either vagus produced the same effect as before the incision was made. Hence it is probable that either the synapse with vagus afferents occurs at the level of vagus entrance, the fibres to the respiratory centres descending in the tract, or the vagus afferents descended before synapsing. In either case the fibres from the tractus solitarius would pass almost medially from the tract to the respiratory cells. The following experiment selected from others, suggests that this is the course of the fibres. In cat b, a transverse lesion was made, cutting into both xii nuclei at a level corresponding Papez 134, about 2 mm. above the obex (plan 2) reaching deep down into the tectospinal tracts and becoming narrower than at the surface. In other experiments, wider sections were made, extending almost to the tractus solitarius at this level. After such sections, stimulation of both vagi were as effective as before the section. Yet such sections would fall below the level of the entrance of most vagus afferents into the medulla, consequently the fibres from nucleus solitarius do not pass medially and caudal to the respiratory cells. Then in this cat a second section was made at a slightly lower level, as shown in plan 2. This section lay about 1.25 mm. above the obex and extended from the surface dorsally to the left margin of the xii nucleus to the ventral margin of the 5th spinal root laterally and ventrally. It
thus cut the left tractus solitarius. This section almost completely abolished any effect of left vagus stimulation. Stimuli of the same strength had no effect, but stronger ones after a longer delay than normal had a slight inhibitory action. This section probably fell below the level of any vagus afferents and consequently either the vagus fibres or the descending fibres from the nucleus solitarius must descend in the tract before leaving it to pass almost medially to the respiratory centre.

SUMMARY

1. The respiratory area appears to lie in the medial third of the medulla from about the level of the junction of middle and upper thirds of the hypoglossal nucleus and is presumably limited below by the pyramidal crossing.
2. Its afferent fibres from the tractus solitarius pass medially from the tract to the respiratory cells.
3. The path descending to the anterior horn cells lies lateral to the anterior horn in the cord.
4. Certain experiments suggest that there may be a crossing of the descending fibres in the medulla at the level of their origin.

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