# THE RELATIONSHIP OF THE VASOMOTOR AND RESPIRATORY REGIONS IN THE MEDULLA OBLONGATA OF THE SHEEP

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That the reticular formation of the medulla oblongata controls the respiratory and vasomotor systems has been established experimentally. Many investiga-tions have aimed at delimiting the medullary respiratory centres (Cordier & Heymans, 1935; Pitts, 1946), but fewer attempts have been made to define exactly medullary regions which influence vasomotor activity (Monnier, 1941; Alexander, 1946). The relationship of vasomotor and respiratory responses elicitable from the medulla oblongata by direct electrical stimulation has received little attention. Pitts, Magoun & Ranson (1939), in their study of respiratory centres in the cat, comment upon the independence of respiratory and vascular responses, since any locus which produced a respiratory response failed to show a simultaneous vasomotor response.

This paper describes the results of experiments in which the medulla ob-longata of sheep was explored systematically and both respiratory and vaso-motor responses were recorded. The results show an anatomical relationship of the respiratory and vasomotor regions, but the function of the two systems appears to remain largely independent.

## METHODS

Scottish Blackface sheep, weighing 20–44 kg under thiopentone sodium anaesthesia were used. Following fixation of the head in a head holder the posterior part of the skull was removed to expose the cerebellum which was removed by gentle suction. The flow of cerebrospinal fluid provided adequate irrigation of the fourth ventricle. Respiration was recorded by connecting the cannulated trachea to a closed circuit spirometer. Blood pressure was recorded from a carotid artery with a mercury manometer.

The electrodes were carried by a stereotaxic instrument (Rosenberg & Tindley, 1949) which offers micrometer movement in three planes and allows the vertical axis to be tilted if required. The bipolar electrodes were constructed from electrolysis needles (Hawkins and Co. Ltd.) having a maximum diameter of 0·23 mm and tapering to a fine point. Each needle was coated with cellulose lacquer leaving a length of 0·25 mm or less of the tip exposed. The twin electrodes were

mounted to leave a gap of 0·2 mm or less between the tips. The insulation of the electrodes was always tested before use.

The stimuli were evenly spaced, brief make and break shocks of alternating polarity (Rosenberg, 1948). The optimum stimulus proved to be 8·3 V at a frequency of 252 stimuli/sec (Bell, 1950). As a rule the test stimulus was maintained for 15 sec. It has been estimated that this stimulus affects a volume of tissue of about 0·5 mm³ (Bell, 1950; Amoroso, Bainbridge, Bell, Lawn & Rosenberg, 1951).

After the experiment the brain was fixed in 10% formol saline and the relevant part of the brain stem sectioned serially. The sections were stained by Weil's method and the individual needle tracts identified microscopically so that the points of stimulation could be correlated with the effects recorded.

## RESULTS

*Respiratory responses*

The nature of the respiratory responses obtained on stimulation showed great variation. These have been discussed in detail already (Bell, 1950; Amoroso, Bell & Rosenberg, 1951). It is necessary here to report briefly the disposition of the maximal responses, i.e. sustained inspiratory and expiratory apnoeas, so that they can be compared with the vasomotor responses from the same locus.

Maximal responses are restricted to the medulla oblongata from the region of the acoustic tubercle to just caudal to the calamus scriptorius. Furthermore, within the medulla the respiratory responses are confined to the medial and lateral reticular formation between the periventricular nuclei dorsally and the inferior olivary nuclei ventrally. The region of respiratory responses can be separated into two divisions, one of inspiratory and the other of expiratory activity.

The maximal inspiratory responses begin rostrally at about the cephalad limit of the inferior olivary nucleus and extend throughout an area in the ventro-medial reticular formation overlying the inferior olive to a level 1 mm behind the obex. At its rostral limit the inspiratory region occupies a thin layer above the inferior olive but it gradually widens posteriorly until at the obex it extends through the whole depth of the median reticular formation. The maximal expiratory responses begin at the level of the acoustic tubercle and are disposed laterally and dorsally to the inspiratory region, extending to the lateral reticular formation, but disappear just behind the obex.

*Vasomotor responses*

A great variety of vasomotor responses were obtained from various areas of the medulla. Examples of typical responses are illustrated in Figs. 1 and 2. Rise of pressure to 200 mm Hg and fall of pressure to 80 mm Hg were found during the experiments, but pressor reactions occurred more frequently than depressor reactions.

As a rule pressor reactions were associated with an increased heart rate, more especially when the rise in pressure was maximal or near maximal. Much

less frequently pressor responses together with slowing of the heart rate were produced, but they were usually submaximal. Depressor responses generally occurred with slowing of the heart.

Vascular reactions began with the onset of stimulation or after a short latent period, the delay being very short when the response was maximal. On cessation of stimulation the vasomotor reactions showed a rapid return to the normal resting level of about 100 mg Hg.
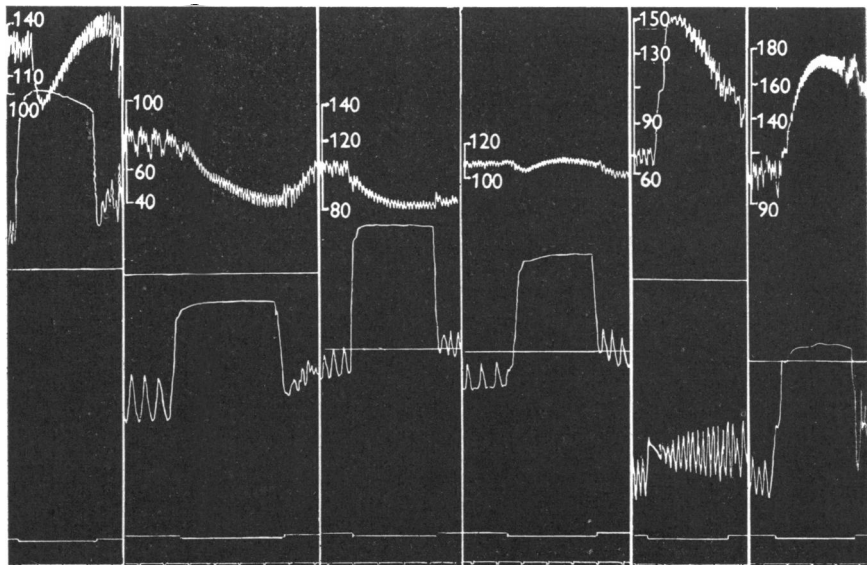


Fig. 1. Variation of vasomotor response when medullary inspiratory region is stimulated at 252/sec and 8·3 V. Records from above downwards, carotid blood pressure, respiration (inspiration represented by upstroke of spirometer), period of stimulation, time marker shows 5 sec intervals.

Maximal pressor responses were first encountered 9 mm rostral to the obex, at the level of junction of the pons and medulla, being confined to an area in the ventral half of the medulla occupying the lateral reticular formation between the medial aspect of the facial nucleus and the descending fascicles of the abducens nerve. This area of maximal response has a fringe of submaximal and minor responses which extend medially in the medial reticular formation as far as the midline. Pressor responses of over 60 mm Hg are met with occasionally adjacent to the median raphe.

More caudally the number of maximal pressor points increases and at the level of the acoustic tubercle, although the grouping is still concentrated in the lateral reticular formation, two wings of responsive tissue pass medialwards to

the midline. The dorsal projection is situated along the floor of the fourth ventricle and the ventral projection overlies the corticospinal tracts somewhat cephalad to the anterior limit of the inferior olivary nuclei. At this level depressor responses of small magnitude begin to appear but are confined to the dorso-medial and lateral aspects of the pressor region.

At a level some 1–2 mm behind the anterior limit of the inferior olive, maximal pressor responses become less frequent, so that depressor responses predominate 2 mm rostral to the obex. The depressor reactions are grouped mainly in the medial third of the reticular formation, as a column which extends from the floor of the fourth ventricle to the inferior olive ventrally and bounded laterally by the fascicles passing from the hypoglossal nuclei. The pressor responses noted at this level are mainly of intermediate degree and continue to be grouped in the lateral reticular formation.

At the caudal pole of the inferior olive, about 4 mm posterior to the obex only minor depressor responses occur from loci in the dorsal half of the reticular formation. At this level the position of pressor responses of 60 mm occupies the same position in the ventral lateral reticular formation as at more rostral levels.

*The interrelations of respiratory and vascular responses*

Plotting the areas of the medulla which show respiratory reactivity and those regions which show vasomotor response shows that both are restricted almost exclusively to the reticular formation, extending from the acoustic tubercle rostrally to a level just behind the obex caudally. The areas showing maximal expiratory reactions, and the areas showing maximal pressor reactions, occupy the same general position in the lateral reticular formation. The regions which yield inspiratory reactions on stimulation also include the regions of the medulla just rostral to the obex from which depression of the blood pressure is obtained.

The correlation of respiratory and vascular responses is not absolute since a variety of combinations of vasomotor and respiratory responses can be observed. Inspiratory apnoeas with variations in the accompanying blood pressure responses ranging from a marked rise to a marked fall, and sometimes no change, were seen.

Fig. 2 illustrates examples of synchronous expiratory and vasomotor responses. The expiratory responses may be associated with many types of vasomotor responses, e.g. hypertension, hypotension and absence of blood pressure changes. Examples of expiratory reaction together with depression of the blood pressure were rare, only very few such dual responses being obtained throughout the series of experiments. Respiratory reactivity without alteration of blood pressure seldom occurred when the reticular formation above the rostral half of the inferior olivary nuclei was stimulated, but anterior

to this region pressure responses without significant respiratory reactions were noted frequently.

Thus the anatomical disposition of the respiratory regions and the cardio-vascular regions show a partial interlocking, the pressor region and the expiratory region occupying the dorsal and lateral reticular formation, the inspiratory and depressor regions both being included in the medial reticular formation
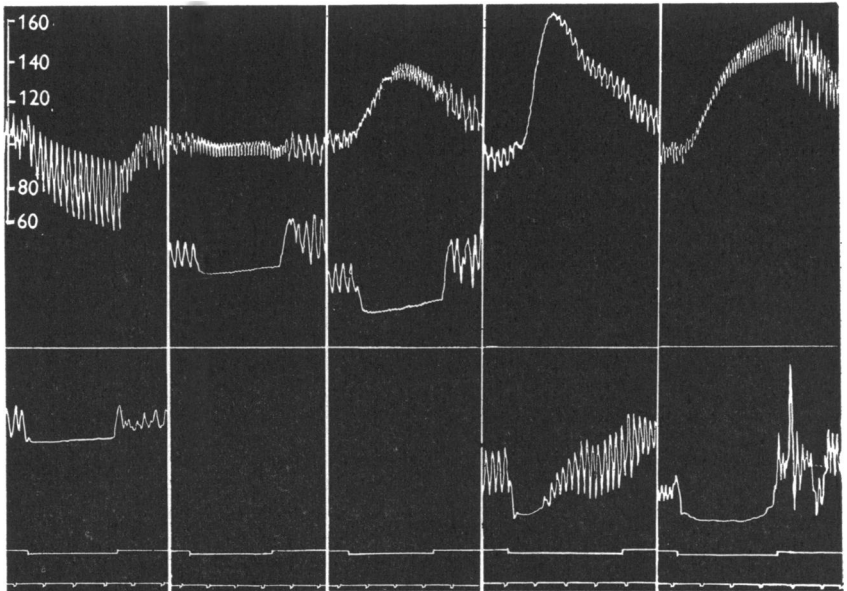


Fig. 2. Variation of vasomotor response when medullary expiratory region is stimulated at 252/sec and 8·3 V.

(Fig. 3). The spatial correspondence of respiratory and vascular areas of the medulla is, however, not complete. For example, the dorsal extension of the depressor region at its caudal limit to the floor of the fourth ventricle is not seen in the inspiratory centre. Furthermore, the inspiratory loci extend more rostrally than the depressor region, but the area of expiratory response is less extensive than the pressor region.

That the blood pressure and respiratory responses are functionally independent is illustrated in Fig. 4. This figure shows vascular and respiratory reactions to stimulation at successive intervals, as the electrodes passed ventrally in stages of 1 mm. It can be seen that although at each level the respiratory response remains constant as a maximal inspiratory apnoea maintained tonically for the duration of the stimulus, the blood pressure traces show variations from a marked hypertension to a slight fall in blood pressure.
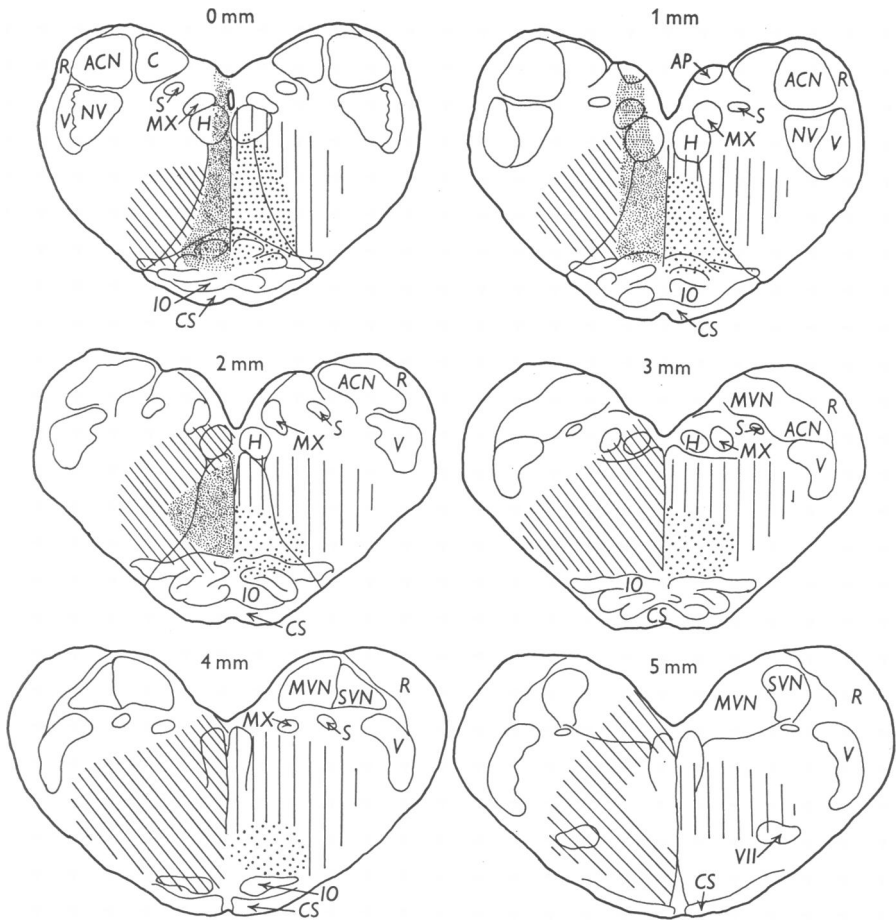
Fig. 3. The interrelationship of vasomotor and respiratory regions illustrated on projection drawings of the sheep medulla. The levels of the transections are indicated in millimetres with reference to the obex as zero. Vasomotor regions are shown on the left side of the diagrams and respiratory regions on the right. Depressor region—fine stippling; pressor region—cross-lines; inspiratory region—coarse stippling; expiratory region—vertical lines. *R,* restiform body; *VII,* facial nucleus; *CS,* corticospinal tract; *MVN,* medial vestibular nucleus; *SVN,* spinal vestibular nucleus; *IO* inferior olivary nucleus; *S,* solitary tract and nucleus; *MX,* dorsal motor nucleus of vagus; *H,* hypoglossal nucleus; *ACN,* accessory cuneate nucleus; *C,* cuneate nucleus; *AP,* area postrema; *NV,* spinal nucleus of trigeminal; *V,* spinal tract of trigeminal.
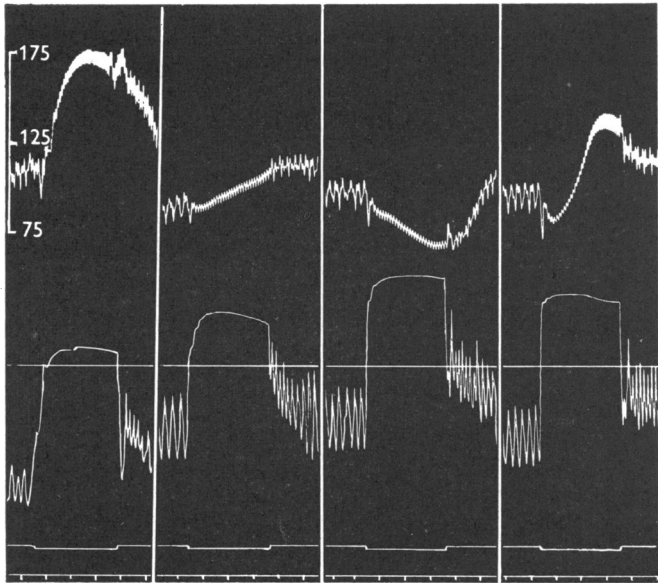
Fig. 4. Variation in blood-pressure response associated with almost similar maximal inspiratory apnoea. The four consecutive records were obtained during the ventral passage of the electrodes in stages of 1 mm. Stimulus 8·3 V at 252/sec.

## DISCUSSION

The areas of the myelencephalon of the sheep which yield vasomotor effects agree in general with those regions of vasomotor activity shown by previous workers in other species. The sheep, like the cat (Wang & Ranson, 1939), shows a region in the reticular formation of the rostral third of the medulla where pressor reactions of large magnitude predominate. In the middle third of the medulla the pressor responses decrease in magnitude and become confined to the lateral reticular formation. At this level maximal fall of pressure occurs when the medial reticular formation is stimulated electrically. Depressor reactions are produced outside the reticular formation at the caudal end of the fourth ventricle, for here stimulation of areas adjacent to the dorsal motor nucleus of the vagus and the hypoglossal nuclei are responsive. This dorsal margin of the depressor region corresponds to the position of the depressor point in the floor of the fourth ventricle of the cat shown by Ranson & Billingsley (1916).

In general, the delimitations of cardiovascular regions in the cat and sheep are in good agreement with regard to maximal responses. Wang & Ranson (1939) and Alexander (1946), using different methods of electrical stimulation, obtained comparable results in defining myelencephalic areas showing vaso-

motor activity in the cat. Alexander used brief condenser discharges with a peak intensity of 8 V at a frequency of 200/sec for routine stimulation. This conforms fairly closely to the stimuli used in the present experiments on the sheep.

Electrical stimulation of the medulla to localize reactive regions might be criticized since in the intact animal the responses produced could possibly be effected by the intra-medullary stimulation of afferent, efferent or internuncial fibres. However, since maximal responses are restricted to certain well-defined regions, it would indicate an excitation of a complex of closely related neurones. Pitts *et al.* (1939) have demonstrated that identical results are obtained by stimulation of the respiratory regions in the intact animal and animals in which the glossopharyngeal and vagal nerves had been sectioned intra-cranially 2 weeks before the experiment. They showed also that decerebration and chronic hemisection of the cervical cord and pons do not affect the response when the medullary respiratory regions are stimulated. These results revealed by stimulation indicate neuronal groupings in the regulation of respiration.

For similar reasons it is permissible to adopt the same technique for the localization of analogous regions controlling the cardiovascular system. That this is the case has been shown by Alexander (1946), who demonstrated that extirpation of the pressor region in the cat produced a reduction in blood pressure and loss of tonic activity in the inferior cardiac nerve. In addition, he found that impulses from the depressor region tonically inhibit the spinal cardiovascular centres. The cardiovascular centres localized by stimulation in both the sheep and the cat thus appear to be functional entities.

The relationship between the cardiovascular and respiratory centres has not been studied in any detail by previous workers. Pitts *et al.* (1939) state that the respiratory and vascular responses obtained by stimulating the medulla of the cat are independent. As evidence they publish two tracings of simultaneous records of respiration and blood pressure on stimulation of the inspiratory and expiratory regions. They suggest that the minimal cardiovascular effects seen may be explained on the basis of mechanical obstruction or as responses to increased carbon dioxide tension in the lungs. In addition they state that the anatomical disposition of the respiratory region differs considerably in extent and location from that shown earlier by Wang & Ranson (1939).

That some areas of the reticular formation, especially in the middle third of the medulla, show interspersed respiratory and vascular loci is apparent in the sheep. It is evident that the effects of stimulation are independent of one another since the grade of vasomotor response does not depend upon the nature of the respiratory response. In the sheep all combinations of respiratory and vascular responses can be produced by stimulating the medulla, and since the vascular effects vary from point to point while the respiratory effect

remains constant, it appears that in certain regions the respiratory and vaso-motor cell groups are intermingled. This statement also probably holds good for the so-called inspiratory and expiratory half-centres, for spike potentials of both types can be recorded in close proximity with microelectrodes in the cat and rat (Amoroso *et al.* 1951). On exploration with stimulation localiza-tion is not strict, i.e. maximal responses demonstrate only regional prevalence of one or another neurone type. That vasomotor and respiratory neurones are interspersed in the same confines completely refutes the concept of circum-scribed centres in the reticular formation of the medulla oblongata. Here the structural arrangement suggests diverse neuronal pools which, according to circumstance, may or may not function independently.

## SUMMARY

1. The myelencephalon of the sheep was explored with stimuli from bipolar electrodes carried by a stereotaxic instrument, the respiratory and vasomotor responses being recorded. The optimal stimulus of 8·3 V at 252 stimuli/sec was used.

2. Respiratory responses can be evoked on stimulation of the reticular formation of the medulla oblongata between the levels of the acoustic tubercle rostrally to the obex caudally.

3. Maximal inspiratory responses occur when the medio-ventral reticular formation above the inferior olive anterior to the obex is stimulated. Maximal expiratory responses were elicited dorsal, anterior and lateral to the inspiratory region.

4. Vasopressor responses of large magnitude predominate in the reticular formation of the rostral third of the medulla, but in the middle third they decrease in magnitude and become more restricted to the lateral reticular formation.

5. Depressor responses are confined to a medial area extending 1–2 mm anteriorly from the obex. This reactive field includes not only part of the medial reticular formation, but also part of the periventricular grey matter.

6. The areas of cardiovascular and respiratory reactivity to electrical stimuli show considerable overlapping.

7. The relationship of cardiovascular and respiratory responses shows that the neurones of these systems are not separable into anatomical entities, although the function of each system remains independent.

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