ACTA NEUROBIOL. EXP. 1973, 33: 311-317
Lecture delivered at Symposium "Neural control of breathing"
held in Warszawa, August 1971

# THE FOETAL AND NEONATAL RESPIRATORY CENTRE: FOCAL STIMULATION AND INFLUENCE OF ANAESTHESIA

V. CHERNICK, A. SKLENOVSKY, R. D. PAGTAKHAN, and V. HAVLICEK

Perinatal Physiology Laboratory, Department of Pediatrics and Physiology, University of Manitoba, Winnipeg, Manitoba, Canada

Respiratory inactivity in utero must be replaced by sustained rhythmic respiration within a few moments after birth. Medullary respiratory structures therefore must be well developed near term. On the basis of indirect studies, Barcroft (1946) suggested that there was active inhibition on the respiratory centre near term and implied that there was a release of inhibition at birth. Burns and Salmoiraghi (1960) have suggested from experiments in the adult cat that foetal respiratory neurones must be quiescent because of a lack of neuronal traffic through the medullary reticular formation. However, we know of no previous direct studies of the foetal medullary structures and therefore undertook to examine the respiratory response to focal stimulation in near-term foetal sheep.

A stereotaxic head holder for foetal sheep was designed and constructed locally. This apparatus allowed us to maintain the foetal head in a central position via metal holders. Preliminary experiments indicated that when the foetal head was maintained in a flexed position at 25° below the horizontal plane the floor of the fourth ventricle was in the horizontal plane and perpendicular to the stimulating electrode.

Near term pregnant ewes (142–147 days gestation) were anaesthetized with sodium pentobarbitone, and the foetus was exteriorized via a Caesarean section, maintaining an intact umbilical circulation. Foetal rectal temperature was maintained between 38.5 and 40°C by means of a heating blanket. A 2.5 cm diameter portion of the occipital bone posterior to

the midline was removed leaving the dura intact. The foetal head was then placed in the holder and stereotaxic co-ordinates were related to coronal and horizontal planes with the external auditory canals as the rotation point and fixed reference axis (Fig. 1).

For the purposes of mapping the foetal medullary respiratory structures up to 14 electrode placements were made in each of the six exteriorized foetal sheep. For each placement the electrode was moved ventrally in 2 mm increments so that 4–5 sites were stimulated. In this manner a total of 350 sites in the brain stems were stimulated in the six foetuses. Stimulation was done with a Grass S8 stimulator in combination with a constant current unit and an isolation unit. Trains of rectangular wave pulses with a frequency of 250 Hz and a duration of 0.5 msec were used. Each site was stimulated for 10 sec with 15 sec allowed for recovery. The initial stimulating current at each placement was increased in 0.15 ma increments until either a respiratory response was obtained or a maximum current of 1.5 ma was reached. All stereotaxic co-ordinates were related to coronal and horizontal planes with the external auditory canals as rotation axis and fixed reference axis. At the end of each experiment the foetal brain was fixed with formalin and the electrode placement checked by macroscopic and histologic examination of the brain stem.

Foetal respiration was monitored by allowing the foetus to breathe saline from a liquid plethysmograph. Changes in pressure within the plethysmograph were recorded and calibrated so that tidal volume could be calculated. Stimulation of the foetal brain stem resulted in one or two inspiratory gasps during the stimulus which varied from 3 to 6 ml, that is, the usual tidal volume associated with liquid ventilation. Occasionally a small expiratory response was obtained ($<$0.5 ml) but this was always associated with generalized muscular contraction and seemed to be non-specific. A deep expiratory response was never seen. Respiration ceased when the stimulating current was withdrawn.

The sites of stimulation and the threshold currents required to obtain respiratory responses in the foetal sheep are shown in Fig. 2; coronal sections through the medulla at the obex, and at 3, 6 and 9 mm rostral to the obex are indicated. The majority of responses were obtained in an area from 3 to 9 mm rostral to the obex, and extended 2 to 3 mm lateral to the midline. Respiratory responses were also obtained from the region of the lower pons. Thus the foetal medullary respiratory structures are quite diffuse and capable of responding to very low stimulating currents.

The results were compared to those obtained from four newborn lambs 3 to 5 days old which were anaesthetized with sodium pentobarbitone. A tracheostomy was performed and respiration was monitored

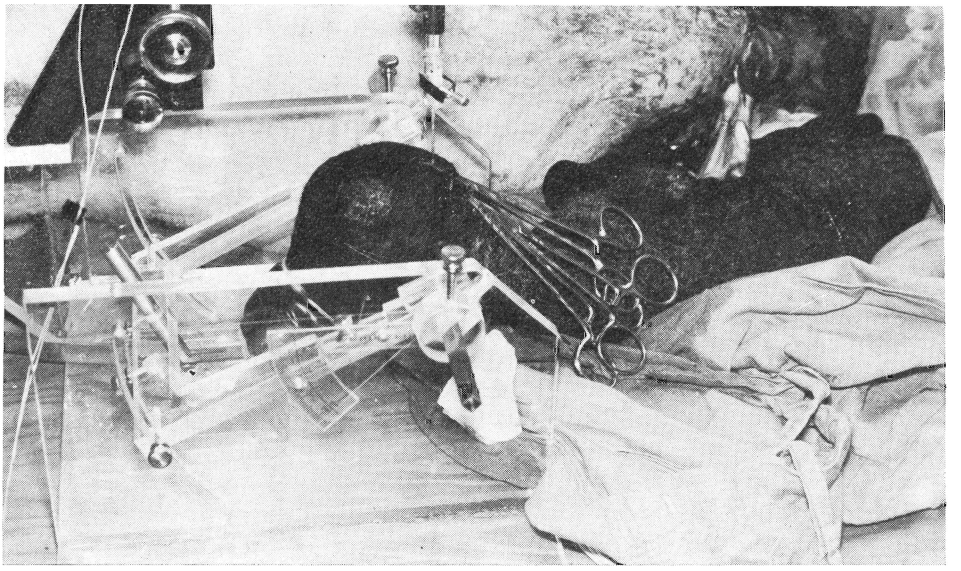

Fig. 1. Exteriorized foetal sheep in stereotaxic head holder. Umbilical circulation is intact.

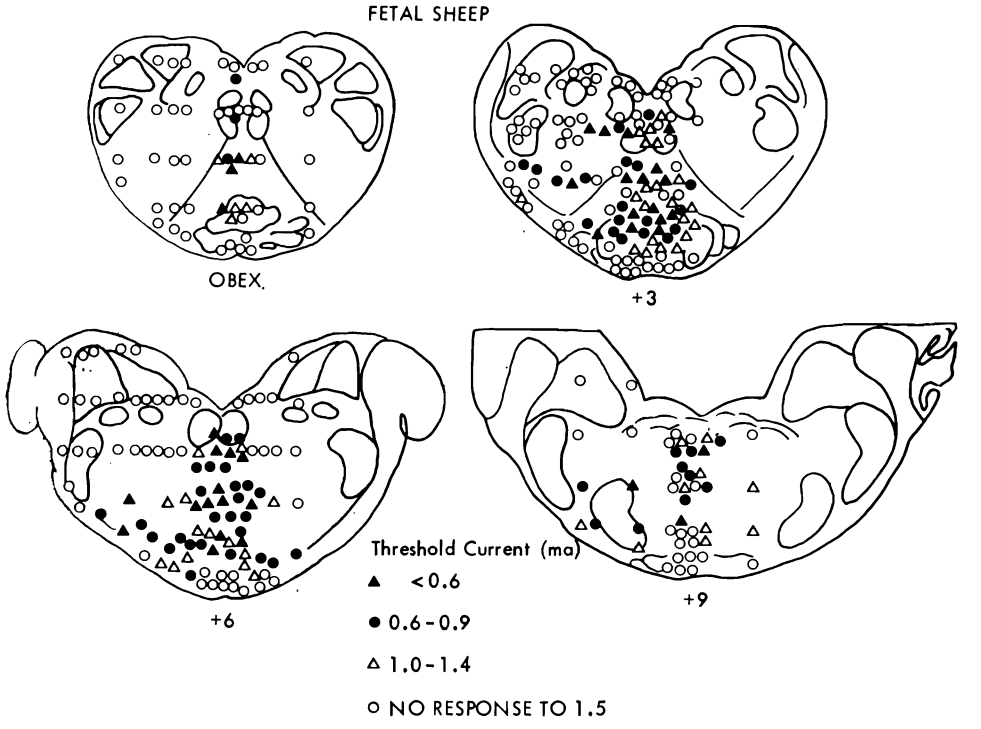


Fig. 2. Coronal sections of the foetal medulla at the level of the obex and 3, 6 and 9 mm rostral to the obex. The threshold currents at various sites are indicated by the different symbols.

by a pneumotachograph and a differential pressure transducer. This method did not allow us to monitor mid-positional shifts in lung volume but the flow trace was integrated to yield breath-by-breath tidal volume. Electrode placements were carried out as described for foetal sheep and a total of 282 sites were stimulated.

The response to focal stimulation of the brain stem of newborn lambs was remarkably different than that of the foetal animal. Increasing stimulating current resulted in a progressive diminution of tidal volume and an increase in respiratory frequency until a current was reached which produced an apnoeic pause. This apnoeic pause occurred at about the same current required to initiate respiration in the foetus and this current therefore was defined as the threshold current. It was always possible to induce an apnoeic pause if there was a decrease in the tidal volume at low currents.

The location of the areas from which an apnoeic pause was obtained in the newborn sheep is shown in Fig. 3. Again four coronal sections

through the brain stem of the newborn lamb and the threshold currents for apnoea are shown from the obex to 9 mm rostral to the obex. The majority of responses occurred at 3 mm rostral to the obex and very few responses were obtained from more rostral sites, in contrast to the results obtained in foetal sheep.

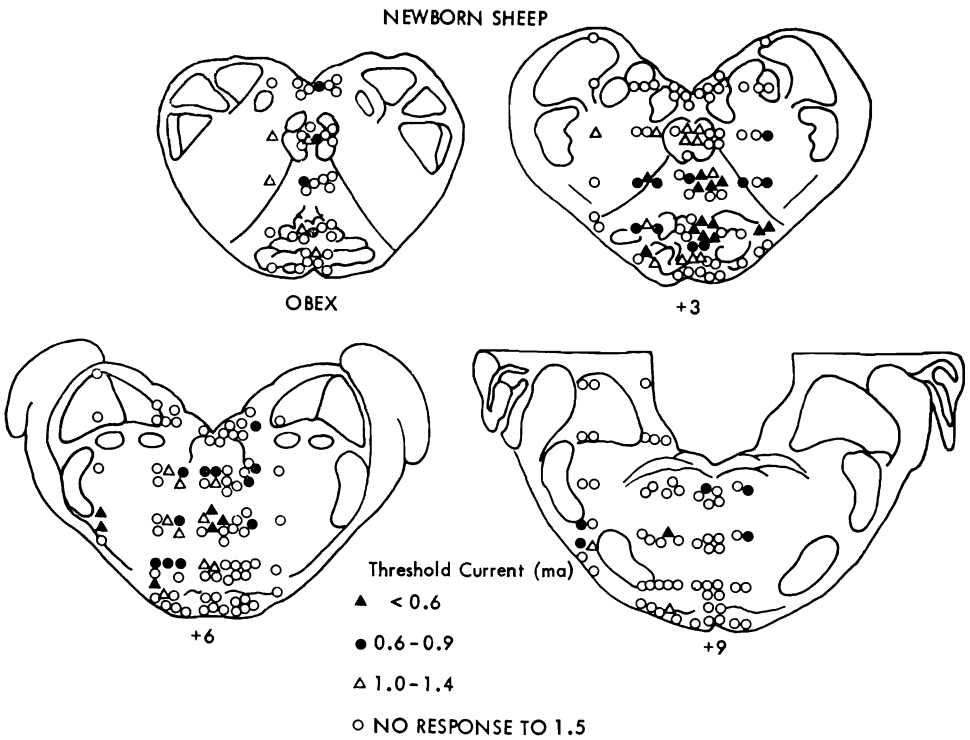


Fig. 3. Coronal sections of the newborn medulla indicating sites and threshold current for a respiratory response.

Figure 4 compares the data obtained from foetal and newborn lambs by a projection of the results onto the dorsal medulla. The respiratory centre as defined by focal stimulation is quite diffuse in foetal sheep, extending from the obex to the lower pons and 2 to 3 mm lateral to the midline. It occupies a volume of approximately 130 $mm^3$. In contrast, the respiratory centre of the newborn sheep is localized to the immediate area of the obex and occupies a volume of about 65 $mm^3$. The respiratory centre of the newborn lamb as defined by the apnoeic pause is similar to the inspiratory centre described by Amoroso, Bell and Rosenberg (1954) in the adult sheep.

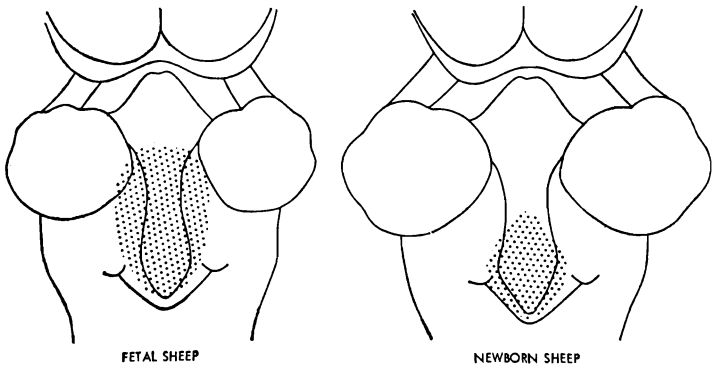


Fig. 4. Comparison of respiratory "centre" of foetal and newborn sheep.

Additional experiments were performed in the absence of pentobarbitone in order to examine the influence of anaesthesia on the threshold current. Near-term pregnant ewes underwent Caesarian section following epidural anaesthesia with 1% lignocaine. Foetal surgery was also performed under local anaesthesia. The stimulating electrode was placed from 3 to 6 mm rostral to the obex within 2 mm of the midline. In newborn lambs all surgery was performed under local anaesthesia and the stimulating electrode was placed between the obex and 3 mm rostral to the obex close to the midline. The results are shown in Fig. 5. In the absence of anaesthesia respiration could be initiated in the foetus at a threshold current of about 0.2 ma. This threshold current was increased by as much as 10 fold in the presence of increasing doses of pentobarbitone. In contrast, in the newborn lamb the presence of pentobarbitone reduced the threshold current required to produce an apnoeic pause.

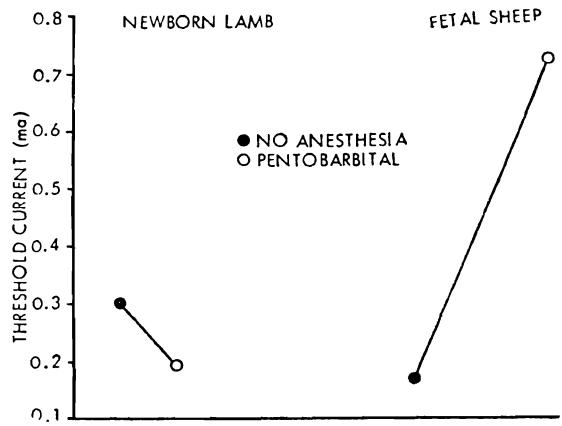


Fig. 5. Influence of anaesthesia on the threshold current in foetal and newborn sheep.

Thus, the influence of pentobarbitone on the respiratory response to electrical stimulation of foetal and newborn lambs is quite different. However, the effect of anaesthesia itself is in fact the same, that is it induces apnoea. The apparently different results however depend upon the initial state of respiration of the animal; apnoea in the foetus *vs.* rhythmic respiration in the newborn lamb.

It is of interest that the exteriorized foetal lamb remains apnoeic as long as placental circulation is intact. This is in contrast to the foetus-in-utero which apparently has rhythmic respiration about 40% of the time (Merlett et al. 1971). It is possible that liquid in the lungs of the exteriorized foetus, now under the influence of gravity, overdistends dependent parts of the lung and foetal respiration is inhibited by vagal afferent discharges. However, we have no direct evidence to support this suggestion.

On rare occasions we have delivered a foetal lamb which exhibited spontaneous rhythmic respiration. We were able to place a stimulating electrode in the brain stem in one such animal. Focal stimulation with 0.6 ma resulted in an apnoeic pause and, following removal of the stimulus, rhythmic respiration resumed. After 90 min the foetus ceased liquid breathing. Following the onset of the apnoeic state, focal stimulation at the same site in the brain stem with 0.6 ma caused one or two inspiratory gasps followed by a return to the apnoeic state after the cessation of the stimulus. This experiment supports our notion that the apnoeic threshold in the newborn lamb and the gasp threshold in the foetal animal are indeed comparable.

In summary, these are the first direct studies of the foetal brain stem respiratory structures that have been reported. Focal stimulation at low stimulating current will induce an inspiratory gasp from a diffuse area in the foetal medulla, suggesting that the respiratory centre is not actively inhibited during the later period of gestation. The major response to stimulation is inspiration in contrast to the apnoeic response of the newborn lamb. The threshold for the initiation of breathing in the foetus increases with pentobarbitone anaesthesia but this agent reduces the apnoeic threshold in the newborn lamb. Thus, the nature of the respiratory responses to electrical stimulation of the brain stem and the influence of pentobarbitone appear to depend on the functional state of the respiratory centre.

**This investigation was partially supported by the Medical Research Council of Canada and the Research Fund, Winnipeg Children's Hospital, Winnipeg, Canada.**

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V. CHERNICK, The Children's Hospital of Winnipeg, Winnipeg 3, Manitoba, Canada.
A. SKLENOVSKY, R. D. PAGTAKHAN and V. HAVLICEK, Perinatal Physiology Laboratory, Department of Pediatrics and Physiology, University of Manitoba, Winnipeg, Manitoba, Canada.