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FETAL BREATHING MOVEMENTS AND SLEEP IN SHEEP

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Résumé

MOUVEMENTS RESPIRATOIRES ET SOMMEIL CHEZ LE FOETUS DE MOUTON. — Bien que l'on soit à peu près certain que le foetus d'agneau plongé dans un bain d'eau salée tiède (mais toujours relié à sa mère par le cordon ombilical) présente de brefs épisodes spontanés d'état de vigilance, il n'y a pas de preuve décisive qu'il en soit de même in utero. Les facteurs qui induisent les mouvements respiratoires foetaux, ainsi que les possibles fonctions homéostasiques de ces mouvements sont discutés en fonction de l'environnement foetal, des échanges gazeux, des stimulations nerveuses et des débits sanguins chez le foetus.

In the past 10 years considerable advances have been made by the use of direct records collected continuously from unanaesthetized foetuses in utero. This has given us a more realistic picture of intrauterine life in some species, notably the sheep. Without the unnatural use of anaesthesia neither mother nor foetus is in a steady state. The periodic variations in foetal behaviour in utero require study as a background to experimental interventions as well as for their own sake. And we also cannot ignore the diurnal variations in maternal behaviour.

Sleep behaviour

Adult sheep.

In laboratory conditions adult sheep sleep for 1-20 minutes at a time, 30-40 times a day, for a total of 4-6 hours (R. Johnson, L. Wilds, unpublished observations). Most of this is slow wave sleep, as judged by the relatively high voltage low frequency electrocorticogram. Rapid eye movement (R.E.M.) sleep, characterised by the presence of vigorous eye movements, a low voltage predominantly high frequency electrocorticogram and the absence of nuchal tone, occurs during sleep episodes and comprises 5-10% of the total sleep time. There is no correlation between maternal behaviour and that of the foetus in this respect (Ruckebusch, 1972).

There appears to be little evidence as to pathophysiological variations in sleep state in sheep in laboratory conditions. For instance, we do not know how ill-health or environmental changes disturb the normal pattern in adult sheep. There is no particular electrocortical pattern associated with rumination (Bell and Itôbisashi, 1973) though movement of the masseters can produce a large
artefact. As in other species there is often a small fall of arterial pressure (by 5-15 mm Hg) during REM sleep, but no systematic changes in the blood gas values.

**Foetal lambs.**

In foetal lambs during the last 0.22 of term, delivered into a warm saline bath but still attached to the mother (under anaesthesia) by an intact umbilical cord, it was possible to recognize quiet sleep, rapid-eye-movement sleep and wakefulness (Dawes et al., 1972). There were also episodes which were not possible to define. The criteria for differentiating these forms of behaviour were similar to those used in newborn infants. It is comparatively easy to discern attention, purposeful movement and abrupt reactions to tactile and auditory stimuli in the foetus after delivery; it is more difficult to differentiate behaviour in utero, especially as between wakefulness and R.E.M. sleep. The difference in electrocortical activity which appears in the foetal lamb near term (Ruckebusch, 1971; Dawes et al., 1972) is gross, varying between 100-200 μV at 3-5 Hz (high voltage slow) and ~50 μV at 15-25 Hz (low voltage fast). The former is a good indicator of quiet sleep, which is normally present rather more than half the time.

To distinguish wakefulness during low voltage fast electrocortical activity in utero, Ruckebusch et al. (1977) recorded eye and body movements. Percussion of the maternal abdomen, during high voltage slow electrocortical activity, caused the appearance of foetal body and eye movements and of low voltage fast electrocortical activity similar to that during waking post-natally. During REM sleep abdominal percussion induced cessation of rapid eye movements and the appearance of some foetal body movements and a slightly larger voltage electrocorticogram. While Ruckebusch et al. (1977) do not specifically state their criteria for recognizing spontaneous episodes of foetal wakefulness, it would appear from their paper that they use a combination of low voltage rapid electrocortical activity, absence of the characteristic rapid eye movements (but not of all eye movements) and the presence of some foetal body movements, often followed by a change in heart rate. The inference is that since these associations are present postnatally they should apply before birth.

In practice these criteria are difficult to apply, since episodes of foetal wakefulness are believed to be so brief (a minute or two) and transitions from one state to another are so indefinite. We need strict criteria for recognising wakefulness in utero, and more information to validate these criteria.

**Criteria for recognising wakefulness in utero.**

Identification of wakefulness postnatally depends primarily on the recognition of attention, abrupt reaction to stimuli or purposeful activity. It is associated with low voltage electrocortical activity, and sometimes with body movements; the rapid eye movements characteristic of paradoxical sleep are absent. There are secondary variations in cardiovascular and respiratory behaviour.

Identification of wakefulness in utero also must depend primarily on the same primary criteria. It will not be easy, it may be impossible, to recognise attention or purposeful activity. We are therefore likely to be left with the reactions to stimuli as a diagnostic tool. We can record the associated phenomena (low voltage electrocortical activity, absence of rapid eye movements, occasional presence of body movements). And we can look for other associations with episodes of putative wakefulness, such as phasic activity in accessory respiratory muscles (intercostal and laryngeal; Harding et al., 1977), and also for the occurrence of such episodes at the end of every third or fourth REM sleep period as after birth (P. Johnson, personal communication). Ultimately such behavioural associations may help in the identification of wakefulness. At present we must rely solely on the primary criteria.

In summary, though we can be reasonably certain that foetal lambs do exhibit brief spontaneous episodes of wakefulness when immersed in a warm saline bath, the evidence that they do so in utero is not yet conclusive. We cannot yet identify such episodes with certainty.

**Foetal breathing movements in utero**

Foetal breathing movements in lambs in utero are predominantly rapid and irregular, in association with low voltage electrocortical activity and when rapid eye movements are
present (i.e. up to about 40% of the time).

In eupnoea (at a P_aCO_2 = 46 mmHg) not all REM sleep is associated with foetal breathing, while in hypocapnia there may be little or no breathing movements present (at a foetal P_aCO_2 < 36 mmHg). Conversely in foetal hypercapnia (P_aCO_2 = 56 mmHg) breathing movements are usually present throughout low voltage electrocortical activity. In these experiments no effort was made to distinguish REM sleep from wakefulness, and it remains to be established whether breathing movements normally are present in the latter state.

The most striking feature of these observations has been the episodic nature of breathing movements before birth. Attention has been directed towards investigating the reasons for this difference from postnatal life. After birth, of course, breathing movements are related to oxidative metabolism through the central and peripheral chemoreceptors, which stabilise the blood gases at values very different from those in foetal life, the P_aCO_2 being lowered and the P_aO_2 raised postnatally. Thus before birth the respiratory system behaves as if it were relatively insensitive to the carotid and central chemoreceptors. Foetal hypercapnia (induced by giving the mother a gas mixture which raises her P_aCO_2 by 8-10 mmHg without affecting P_aO_2) makes foetal breathing movements, when present, more regular in rate and increases their depth. Several other kinds of respiratory stimuli have been examined.

Stimulation of the central end of a mixed nerve (e.g., the sciatic) is well known to stimulate breathing movements postnatally. Before birth the evidence has been controversial. Bystrzycka et al. (1975) concluded from experiments on anaesthetized and exteriorized foetal lambs that sciatic nerve stimulation was ineffective, while Condorelli and Scarpelli (1976) in partly exteriorized lambs found that it caused slow regular breathing movements, often sustained for a long time after stimulation had ceased. If this were true in utero we might expect that tactile stimuli would excite episodic breathing movements; yet slow regular breathing movements are most uncommon in normal foetal lambs in utero.

Our own experience on unanaesthetized chronic foetal lamb preparations has been different from either of these two reports. Electrical stimulation of the sciatic or median nerve, at a strength sufficient to cause a small sustained rise of arterial pressure (< 5 mmHg) had variable effects hour by hour in the same lamb (Chapman et al., 1977). Sometimes, if the foetus was already making breathing movements, these became faster and more vigorous or, if originally in apnoea, breathing movements appeared which were unrelated to the stimuli. Both were regarded as a positive response. At other times the foetus did not respond, or such changes in tracheal pressure (positive or negative) as appeared were entrained with the stimuli (classified as negative responses). The incidence of positive responses was 19% on average in 9 lambs; the breathing movements rarely persisted for more than a few seconds after the end of electrical stimulation. If stimuli were applied during high voltage slow electrocortical activity this changed to predominantly low voltage fast activity and, if the foetus was in a warm saline bath, there was visible evidence of arousal. This seems to be the only direct evidence to suggest that foetal breathing movements may be present during arousal or wakefulness. The difference from the observations of Condorelli and Scarpelli (1976) must be attributed to the experimental conditions, which in their case may have been associated with cooling the foetus, a well verified cause of respiratory stimulation long before normal term.

It is incidentally worth noting that cooling foetal lambs, either restrained on a table adjacent to the ewe (Dawes, 1968) or in a saline bath, induces regular breathing movements. These are normally slow unless tracheal pressure, and hence lung volume, is reduced (i.e. the pulmonary stretch receptors are active from 110 days gestation or earlier). They are thus very different in character from normal irregular, rapid prenatal breathing movements in association with REM sleep. Preliminary studies in which ice-cold saline solution (50-300 ml.) was introduced into the amniotic cavity in utero has shown this as inconstant an effective stimulus to foetal breathing as electrical stimulation of a peripheral nerve. On the contrary foetal injection of drugs which excite carotid chemoreceptors, such as lobeline or nicotine, invariably initiates a brief episode of deep inspiratory efforts. The failure of the foetal lamb to exhibit breathing movements in quiet sleep is therefore not due to
an irresistible inhibition of respiratory activity.

**Foetal breathing and homeostasis.**

Rapid irregular foetal breathing movements in REM sleep are accompanied by collapse of the chest wall; the intercostal muscles are not normally active. But all the accessory muscles of respiration are involved when the foetal gasps. If breathing is purely diaphragmatic there should be less metabolic demands on the foetal respiratory system (i.e. on respiratory gas exchange across the placenta). It was tempting to suppose that, during hypoxia, the arrest of all breathing movements (Boddy et al., 1974) would provide an advantage for survival by reducing the requirement for 02. However foetal asphyxia usually involves hypercapnia and acidemia as well as hypoxemia, and in these conditions breathing movements may be continued for many hours at a time, albeit at a reduced frequency (~ 20/min) and depth (Patrick et al., 1976). In this respect the system is not well-designed to maintain the internal environment.

One of the striking observations of the past few years has been of foetal lambs which, for days at a time, have survived in utero with abnormally low PaCO2 and PH values and, to a lesser extent, a raised PaCO2. This deviation from normality is usually accompanied, as expected, by a rise in plasma catecholamine and vasopressin levels and sometimes, but not always, by abnormalities in arterial pressure and heart rate sufficient to be identified. On the other hand we have often encountered, over the past 7 years, lambs with an abnormally low carotid PO2 (10-14 mmHg), with normal PCO2 and pH values, in which the incidence and pattern of foetal breathing appeared normal. These lambs always had a packed cell volume >50%, well above normal (32.6±0.9 S.E.% in 50 lambs, 95-146 days gestation). The O2 carrying capacity of their blood was raised, presumably in response to chronic hypoxaemia. The presence of normal foetal breathing suggests that compensation was adequate, that the O2 content of the arterial blood was sufficient to maintain normal function.

**Foetal breathing and inferior vena caval flow.**

The integration of physiological functions is complex. Recently a new point has arisen about the distribution of cardiac inflow in relation to foetal breathing.

Using an ultrasound transducer continuously activated at 2 MHz, Doppler shift frequencies synchronous with foetal breathing movements were detected in man (Boyce et al., 1976). In foetal lambs near term directional analysis showed that high velocities, in phase with inspiration were directed cephalad (Gough and Poore, 1977). Measurements from a catheter-tip mounted ultrasound transducer, operated at 10 MHz to measure local flow velocities and introduced through a femoral or jugular vein, confirmed the conclusion that these arose from the inferior vena cava and hepatic veins near the diaphragm. The peak flow velocities were usually well in excess of 1m/sec. On expiration there was often reversed flow in the inferior vena cava.

It can hardly be doubted that with such high flow velocities in the vena cava (and perhaps venous collapse), mixing of the blood streams in the great veins will be much facilitated. We shall therefore need to reconsider this old question, which has been so often debated over the past two centuries. You will remember that Sabatier (1778) suggested that the foetus might be better off by preferential direction of well oxygenated blood from the placenta via the left ventricle to the ascending aorta, and hence to the heart and brain. Huggett in 1927, 50 years ago, established that carotid arterial blood contains more oxygen than that in the descending aorta. But subsequent measurements in vivo have suggested that the difference between the two is small. Whether there is indeed a measurable change in this difference with foetal breathing, or in the distribution of cardiac output between the two sides of the heart, remains to be established.

In conclusion we are still left with several questions which are only partly answered. Why does the foetus breathe before birth? No gas exchange takes place. This prenatal isometric practice may ensure that the diaphragm is strong at birth and that the lung is properly grown. We do not yet understand the mechanism(s) by which continued
breathing in quiet sleep is maintained postnatally but not prenatally.

Are foetal REM sleep and breathing linked to endocrine functions? They certainly have a diurnal rhythm, but neither our own studies nor those of others have yet established a direct link with growth hormone, ACTH or cortisol, for instance. There is an inverse correlation between the incidence of foetal breathing movements and foetal plasma ACTH concentrations (Boddy et al., 1974), but this was probably a result of the variable incidence of hypoxaemia in these sheep, since hypoxia has been shown to lower the former and raise the latter.

References


