Maternal endocrine situation and fetal behaviour: possible correlation mechanisms
Proplomelacortin - B-endorphin - Cortisol


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It has been known for a long time (Precht, 1974) that the fetus - as the pregnancy comes to an end - acquires a behaviour similar to that of the newborn.

Moreover, the cardiocographic studies (Timor-Trish et al, 1978, Romanini et al, 1983), associated with the ultrasonic ones (Nijhuis et al, 1982, Arduini et al, 1985) have broadly demonstrated the existence of circadian rhythms concerning the major fetal movements (FM) (Patrick et al, 1982), the respiratory movements (Patrick et al, 1980) and the variability of the fetal cardiac frequency (Visser et al, 1982).

Although different hypotheses were formulated to explain these attitudes, it should be added that the existence of endocrine and behavioural biorhythms has been evidenced experimentally.

The fetus, in particular, represents from this point of view a very special model, given that a large part of its behaviour may be determined and/or affected by the maternal endocrine mechanisms.

Some experimental data do prove, in fact, the hypothesis that both these systems are interactive:
1) The fetal activity index features a daily distribution similar to that of E3 (Patrick et al, 1982)
2) Plasma cortisol shows a biorhythm which is exactly the inverse of that of cortisol in the mother (Patrick et al, 1980);
3) The administration of cortisone to the mother before the 38th week of pregnancy leads to a loss in the circadian variations and to a considerable increase of the activity index (Arduini et al, 1985)
4) Maternal stress causes an initial condition of fetal hyperactivity which is then followed by a fetal hypo-activity phase (Ianniruberto, 1981).

Such experimental premises lead to two hypotheses and considerations:
- Fetal behaviour is affected by the maternal neuro-endocrine modifications.
- Cortisol is at least one of the regulation and interaction factors.

It must of course be said that although the encephalus activity is extremely sensitive to the endocrine environment
(Etigi et al., 1978), the latter is also conditioned by numerous other factors.

We know that in the case of Cushing's disease adults are usually depressed, but on the other hand, in the exogenous cushingoid there is usually euphoria. It may be thus hypothesized that the activating mechanism does not lie in cortisol itself, but in some other point of the hypothalamus-hypophysis-suprarenal axis.

Neuroregulatory control mechanisms both neurotransmitters and neuromodulators such as DOPA and 5HT probably do play a role in this; DOPA and 5HT affect the tone of the Corticotropin-Releasing Factor (CRF) and Proprio-Melanotropin (POMC).

Further proof of the fact the cortisol mechanism is only partially responsible for fetal behaviour is, as previously stated, the clear contradiction constituted by the increase in fetal movement during the administration of cortisones or under stress conditions and, on the other hand, fetal behaviour under basal conditions, a behaviour which is characterized by a decrease in activity during morning hours (when cortisol contents in the mother are high) and an increase in activity at night (when cortisol contents in the mother are low).

Therefore when cortisol is administrated and it rises quickly (stress) a fetal activity increase is observed which can be explained in the diagram illustrated in fig.1. It shows at the end a reduction in the ß-endorphin and thus an activity disinhibition.

Such mechanism is of absolutely no use in explaining the opposite behaviour in basal conditions.

The state of immobility could be at least partially explained by the increase of endorphins. Experimentally, in fact, the injection of 50H-triptamine into the brain of sheep fetuses produces a state of restful sleep (Jouvet, 1967) and also increases the ACTH, hence also the POMC and ß-endorphins. However, it's difficult to say whether such restful sleep mechanism only accompanies the endogenous morphine increase or is the consequence of it.

ß-endorphin increases progressively in fetal blood during the whole pregnancy period (Wardlaw, 1979), reaching at the end of gestation, values about four times higher than those found in normal adults (Facchinetti, 1982).

Experimental data on sheep demonstrate there is an association between hypoxia and fetal distress and ß-endorphin (Wardlaw, 1981) but it is not certain whether ß-endorphin is the cause of a reduction in fetal movement or whether it only accompanies such a reduction as a consequence of asfixia.

In this respect it should be noted that Cherneck(1982) has proved that the administration of Naloxone (the specific antagonist to ß-endorphin) improves the conditions of rabbit fetuses made hypoxic experimentally, and it increases their Apgar score at birth.
Fig. 1 - A maternal stress determines an increase (NE) and reduction (DA) of neuroendocrine mediators, that produces an increase of POMC peptides. The increase of ACTH stimulates cortisol (F) and cortison (E) production. Those hormones cross through the placenta where E is converted in F. The F inhibits fetal POMC owing a reduction of fetal ACTH, fetal CLIP and fetal βEP. The reduction of βEP realises an increase of fetal activity. It seems so explained the old clinical impression that a maternal stress creates a strong activity in the fetus. NE = Nor-epinephrine; DA = dopamine; POMC = Proopio-melano-cortin; CLIP = corticoid liberator intermediate peptide; βEP = β-endorphin.

Whatever the etiological mechanism might be, one of the deciding factors in fetal activity is no doubt endogenous morphine.

Endogenous morphines are produced in particular by the fetus (Wardlaw, 1979), while the mother does not transfer her own endorphins to the fetus (Cacontos, 1979; Goland, 1981). The placenta would instead provide peptides and ACTH similar activities and β-endorphins in the amniotic fluid.
(Krige, 1982), though such choridal production cannot be said to play any role in the physiology of the maternal-fetal hypothalamus-hypophysis-suprarene axis.

A particularly important factor is the loss of control of the secretion of cortisol on the part of the fetal suprarene and $E_3$, after the 36th week of gestation. This loss is probably related to the increase in the fetal suprarene mass which according to various authors (Jackson, 1909; Spector, 1956; Kondo, 1959) increases decisively going from 3-5 grams at 35 weeks to 8-10 grams at the end of pregnancy.

The volume increase of the suprarenal mass is however limited to the so-called fetal area, a structure typical of intrauterine life, which quickly involutes after birth and which, according to some authors (Silman, 1976 and 1978), would be directly controlled by the intermediate hypophysial portion that is also bound to the spontaneously reabsorbed after birth.

On the other hand, although the relation $E_3$/cortisol cannot be investigated after the 35th-36th week, neurological biorhythms are not modified by the same.

It is in fact possible that maternal conditioning (via cortisol) continues to be active even when the inhibition on the steroid synthesis of the fetal suprarene is lost. This is probably made possible by the fact that the fetal area does not secrete large quantities of cortisol which could add to the maternal one. It would be quite impossible for this to happen as the fetal suprarene lacks the fundamental enzymatic activity constituted by 3B-HSD (3β-4 isomerase).

In this way the fetal suprarene goes on producing limited amounts of cortisol and the cortisol levels in the mother will always be 8 to 10 times higher than those in the fetus (Gibson, 1980).

Moreover, although the "diffusible cortisol" (that which is linked to the CRC and not conveyed by the albumins) represents the lesser amount of cortisol in the mother, the diffusion gradient is always at least 3:1 (Campbell, 1977). This proportion stays high till the end of gestation when the cortisol amount in the mother — which is transformed into cortisone in numerous parenchymals (fetal lung and chorion) by means of an 11-dehydrogenase — remains integral due to the decrease in this enzymatic activity and the increase in the opposite activity (11-ketoreductase) which is capable of carrying out the cortisone-cortisol transformation.

On the basis of studies effected on radioisotopes (Sittins, 1979), it is calculated that the maternal contribution to the fetal cortisolemia varies at the end from 25% to 50%, and for the cortisone it is about 100%.

The fetal suprarene produces instead ever-increasing amounts of DHEA-5 which only after passing into the choroidal area will find those specific enzymatic activities (3B-HSD,
sulfatase, aromatase) capable of converting it into progesteron and corticoids.

The above mentioned considerations justify the hypothesis that fetal behavior is in some respects correlated to the maternal-fetal endocrine condition and that the hypothalamus-hypophysis-suprarenal axis of the mother and the fetus are interactive.

This is only one of the aspects of the complex mechanism which regulates such behaviors and which undoubtedly involves in the process many other glands and controls of the central nervous system.

What today appears as a hypothesis can therefore be considered as just the tip of an iceberg which the present studies on fetal behavior have brought to light.

REFERENCES

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