Fetal Neuroendocrine Mechanisms in Development and Parturition

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INTRODUCTION

The study of the factors influencing intrauterine growth and labor might contribute towards the understanding of disturbances in these processes and so towards the reduction of perinatal mortality and brain traumata that are caused by these disturbances (e.g. Roberts and Thomson, 1976; Alberman, 1976). Recent investigations make it probable that, of the various factors involved in intrauterine growth and parturition, the fetus itself plays an important role by means of neuroendocrine mechanisms.

In some species, for example in birds, there is no question about the importance of the fetus itself in such processes. The chick fetal brain and pituitary are stimulating growth (for references see Thommes et al., 1973), while the forebrain controls the final stage of hatching (Corner et al., 1973; Sohal, 1976). But not in all species are fetal factors so clearly separated by an egg-shell from maternal and environmental factors. In mammals, where environmental, maternal, placental and fetal factors are strongly intermingled and inter-related, the importance of the fetal component cannot be defined easily. In order to study to what extent the human fetal brain is involved in the control of fetal growth and parturition, observations were performed in anencephaly and other congenital brain anomalies. Although these studies suffer from all the drawbacks inherent in pathological material, it is the only available means of obtaining data on this subject in man. Therefore, hypotheses arising from these observations are tested experimentally in rat, while mechanisms found by such experiments are in turn examined for their presence in man. The evidence for fetal neuroendocrine mechanisms in intrauterine growth and birth in man and rat are reviewed in the present paper.

THE FETAL BRAIN AND INTRAUTERINE GROWTH

Human congenital brain anomalies and intrauterine growth

Jost (e.g. 1954) has emphasized that the fetal brain and pituitary are not of importance in intrauterine growth because growth does not stop in human anencephalics and in fetuses of various other species after decapitation. This is only partly true because, generally, a decreased growth rate is observed after such lesions (Honnebier and Swaab, 1973; Swaab and Honnebier, 1973, 1974) (Fig. 1a, d).

Normal fetal growth in man shows an S-shaped course with an acceleration of the growth

rate at about 20 weeks of pregnancy (e.g. Swaab et al., 1977b). This 'growth spurt' is dependent on the integrity of the fetal brain, as appears from (1) the low birth weight in cases of spontaneous decapitation during the first trimester (Liggins, 1974) and (2) of anencephaly (Honnebier and Swaab, 1973) (Fig. 1a), (3) from clinical data on growth arrears in anencephalics (Swaab and Honnebier, 1974) and (4) from the low birth weight of microcephalics in which the hypothalamus was absent (Janigan et al., 1962). In addition, (5) a normal birth weight was observed in one case of hydranencephaly which had an absent cerebrum but intact brain stem (Liggins, 1974). All these data point to the importance of an intact hypothalamus for normal intrauterine growth in man.

The difference at 40 weeks of pregnancy between the mean anencephalic birth weight and the normal mean (i.e. the 50th percentile line) in our material is considerable: about 1000 g on a total corrected normal birth weight of 3000 g (Fig. 1a). The difference in lean body weight might even be greater since the anencephalics have an increased mass of subcutaneous fat (e.g. Bearn, 1971). The decreased body weight in anencephalics of 1000 g is an important difference as compared with, for example, the well-known serious fall in body weight observed in very severe undernutrition. The decrease in birth weight during the Dutch famine (1944–1945) was 200 g, and during the second world war siege of Leningrad the birth weight decrease was 400 g (Winick, 1976). The growth impairment in anencephaly cannot be explained by the fact that all kinds of congenital anomalies are growth retarded, since the reduction of body weight in other kinds of serious congenital anomalies was much less extreme than that in anencephalics (Swaab and Honnebier, 1974). Data strikingly similar to ours in anencephalic children (Fig. 1a) were obtained by Kittinger (1977) in the

Fig. 1. Retarded intrauterine growth in the absence of the fetal brain in man (a), rhesus monkey (b), chick (c) and rat (d). a: upper broken line = 50th percentile line of the control group; lower broken line = same line after subtraction of the brain weight. The linear regression lines for male and female anencephalics are based on Honnebier and Swaab (1973). b: reproduced from Kittinger, 1977, with permission of the Ciba Foundation. c: body weights of normal and in stage 11–13 decapitated chick embryos (with permission after Case, 1952). d: body weight of rat fetuses which were sham operated (arrow) on day 19 (S) or brain-aspirated (ASP) on day 19 of pregnancy (data calculated from Swaab and Honnebier, 1973).

rhesus monkey (Fig. 1b). Following surgical encephalectomy or decapitation at about 75 days of gestation, fetal growth was delayed in a similar way as in anencephaly.

The fetal rat brain and pituitary in growth

Also in the rat the fetal brain is stimulating intrauterine growth. During normal intra-uterine development fetal growth in rat shows a sudden acceleration at day 19 of pregnancy. This 'growth spurt' appeared to be absent in rat fetuses from which the brain and pituitary had been removed (Swaab and Honnebier, 1973) (Fig. 1d). After removal of the fetal brain and pituitary, fetal body weight is lower than after removal of the fetal brain alone (Table I).

The minor difference between these last two groups shows that the pituitary is to a high degree dependent on the fetal brain for the stimulation of intrauterine growth. Removal of the fetal brain and pituitary in this experiment (Table I) decreased the body weight 18% against more than 25% in earlier experiments (cf. Swaab and Honnebier, 1973). This difference in size of the effect might be due to compounds crossing from the intact fetuses to the operated ones in the present experiment, which was not possible in former experiments in which the entire litter was treated in the same way.

The hypothalamus seems to be an essential structure for normal fetal growth, since a reduction in fetal body weight has also been found after selective destruction of the fetal rat hypothalamus, but not after destruction of other brain areas (Fujita et al., 1970). Fujita's experiments showed, in addition, that such growth rate changes following brain lesions were not due to the duration of the surgical procedure, amniotic fluid loss or uterine damage as suggested by Rieutort and Jost (1976) since all these factors were the same in his experiments.

In order to test the possibility that humoral factors of hypothalamo-hypophysial origin play a role in the regulation of intrauterine growth in rat, pituitary hormones and hypothalamic extracts were injected directly into rat fetuses from which the brain and pituitary had been removed. No stimulation of intrauterine growth was obtained with any of the following compounds: growth hormone, ACTH₁₋₂₄, ACTH₄₋₁₀, TSH, prolactin, LH, FSH, HCG, oxytocin, hypothalamic extract (fraction C), insulin, placenta extract and cyclic AMP (Swaab and Honnebier, 1974; Honnebier and Swaab, 1974; Swaab et al., 1977b). The only factor which was found to stimulate intrauterine growth was the hormone of the intermediate lobe of the pituitary, α -MSH (Honnebier and Swaab, 1974; Swaab and Honnebier, 1974).

TABLE I
FETAL BODY WEIGHT IN RAT (IN PERCENTAGE ($\pm$ S.E.M.) OF SHAM OPERATED CONTROLS) AFTER REMOVAL OF THE PITUITARY AND/OR THE BRAIN

In each of 7 rat litters the fetuses were divided at random at day 19 of pregnancy in operation group I, II or III (for operation procedures see Swaab and Honnebier, 1973). Body weight was determined at day 21 of pregnancy and expressed as a percentage of the sham-operated controls which had a mean weight of 4.49 ± 0.091 g. The absence of pituitary and/or brain was checked by means of a stereomicroscope on a midsagittal section through the fetal head. In the entire group one fetus died and two could not be placed into one of the three groups. The differences between I and II and II and III are highly significant (Student's *t*-test = $P < 0.001$).

I	Sham operation (needle only stabbed into cerebrum)	(n = 30)	100	(± 1.23)%
II	Removal of the fetal brain (leaving the pituitary intact)	(n = 27)	85.3	(± 1.58)%
III	Removal of the fetal brain and pituitary	(n = 25)	81.9	(± 1.42)%

MSH and intrauterine growth

Evidence is accumulating that the growth promoting effect of α -MSH is indeed a physiological function of this hormone in the fetus. MSH is detectable by means of bioassay and immunofluorescence in the fetal rat pituitary from day 18 of pregnancy, i.e. one day before the intrauterine growth spurt starts (Swaab et al., 1976), while by means of radioimmunoassay α -MSH was found in the fetal pituitary and amniotic fluid already on day 17 of pregnancy (Thody, unpublished observations). Moreover, a significant negative correlation was found between the pituitary content of bioassayable MSH and fetal body weight on day 19 of pregnancy (Swaab and Visser, 1977), suggesting an earlier onset of hormone release in the heavier fetuses. That endogenous fetal α -MSH has indeed a function in stimulating intrauterine growth appeared, in addition, from the growth inhibition following injection of purified anti- α -MSH plasma directly into the fetuses on the day of the intrauterine growth spurt (Swaab et al., 1976; Swaab et al., 1978).

MSH and brain development

The body of evidence increases that those endogenous compounds which affect behavior in adult organisms are necessary for normal brain development. This holds true for the thyroid hormones (cf. Querido et al., 1978), sex hormones (cf. Van de Poll et al., 1978) and neurotransmitters (Lewis et al., 1977).

There are various arguments in support of a possible involvement of α -MSH in adult brain function. α -MSH and related compounds were found to have important behavioral effects (for review see Van Wimersma Greidanus, 1977). Such central effects are also reflected by the influence of MSH on the electrical activity of the nervous system (for references see Kastin et al., 1973). In addition, rat nervous tissue has been shown to contain MSH activity (Rudman et al., 1974) which was confirmed by us using a radioimmunoassay for α -MSH (unpublished observations). The compound present might be either α -MSH itself (Oliver et al., 1977) or an α -MSH-like compound which was found by means of immunofluorescence (Swaab and Visser, 1977) and, more recently, by an immunoperoxidase technique (unpublished observations) to be localized throughout the rat nervous system. It has also been suggested that both related compounds are present (Vaudry et al., 1976). Since the α -MSH-like compound remains measurable (Vaudry et al., 1977) and visualizable (Swaab and Visser, 1977) after hypophysectomy, it is more likely to be synthesized in the nervous system itself than in the intermediate lobe of the pituitary. Because of the neurotropic effects of α -MSH in adults and its involvement in fetal body growth, the involvement of this hormone in brain development is currently being investigated. Injection of anti- α -MSH subcutaneously into the rat fetus induced not only a decrease in fetal body weight, but also a decrease in brain wet- and dry weights, protein and lipid contents, while brain DNA remained unaffected (Swaab et al., 1978). These data point to a role of α -MSH in nerve cell differentiation rather than in multiplication.

MSH in human development

In order to see whether a growth promoting role for α -MSH might exist in man, a study is currently being carried out in the human fetus. By means of immunofluorescence microscopy, α -MSH was indeed found in the intermediate and anterior lobe of all 6 normal fetuses that have been studied so far between 15 and 20 weeks of pregnancy (Visser and Swaab, 1977). This agrees with the data of Silman et al. (1976) who assayed α -MSH radioimmunologically after chromatographic isolation. No intermediate lobe is present in the majority of anencephalics (Angevine, 1938). In the two anencephalics that we have examined until

now by means of immunofluorescence, no α -MSH could be demonstrated in the anterior pituitary (the only part of the hypophysis that was present in these newborns) (Visser and Swaab, 1977). Since anencephalics show a lower intrauterine growth rate (Honnebier and Swaab, 1973), and have probably lower MSH levels in blood (Honnebier and Swaab, 1975), α -MSH might well play a role in intrauterine growth also in man. The absence of α -MSH in the pituitary of human anencephalics and its presence in normal human fetuses would, moreover, point to the fetal brain as the structure which is necessary for the appearance of the intermediate lobe and α -MSH in development.

THE HYPOTHALAMO-NEUROHYPOPHYSIAL SYSTEM (HNS) IN DEVELOPMENT

The fetal HNS and water balance

A second neuroendocrine system which might be of importance during development in the fetus is the HNS. Neurohypophyseal hormones are already present before term. In rat neurohypophysis axons appear between day 17 (Galabov and Schiebeler, 1978) and 18 (Paull, 1973) of pregnancy, while oxytocin and arginine vasopressin (AVP) were found by radioimmunoassay in the fetal pituitary from day 17 of pregnancy (Forsling, 1973). In the human fetal pituitary AVP was found radioimmunologically from 12 weeks of pregnancy (Skowsky and Fisher, 1973), while quantitative bioassay estimates of oxytocin and vasopressin activity became possible at 16 weeks of pregnancy (Dicker and Tyler, 1953). Immunofluorescence was found using either unpurified or purified antibodies against oxytocin and vasopressin in the human fetal neurohypophysis from 15–16 weeks of pregnancy (Fig. 2).

Characteristic for the fetal neurohypophysis in all species studied to date is the high vasopressor to oxytocic ratio. According to Perks and Vizsolyi (1973), this might indicate that the supraoptic nucleus becomes active earlier in development than does the paraventricular nucleus. This hypothesis, however, is based upon the assumption that the supraoptic nucleus would synthesize mainly vasopressin and the paraventricular nucleus mainly oxytocin; this has been proven not to be the case. In the adult rat, both nuclei show the

Fig. 2. Immunofluorescence in the neurohypophysis (NH) of a human fetal pituitary of 16 weeks of pregnancy (code B), using unpurified anti-vasopressin (#126) (a) and anti-oxytocin (#02D) (b) (for technical details see Swaab and Pool, 1975). The horizontal bar represents 100 μ m.

same ratio of oxytocin- to vasopressin-containing cells (Swaab et al., 1975). In their study on the nature of fetal seal neurohypophysial hormones, Perks and Vizsolys (1973) found a principle with high frog bladder activity. Together with the amino acid analysis, this finding made it most probable that the fetal neurohypophysis contained, as a third hormone, arginine-vasotocin (AVT), a peptide hitherto thought to be confined to lower vertebrates (Heller and Pickering, 1960; Sawyer, 1966). AVT was reported also to be present in the pituitary of the fetal sheep (Vizsolys and Perks, 1976; Skowsky and Fisher, 1973), the human fetus (Skowsky and Fisher, 1973) and the rat fetus at term (Swaab et al., 1977b).

New observations make it improbable, however, that the compound that was measured in the fetal rat pituitary is indeed AVT. Recently we have produced antibodies against AVT that permit a sensitive (up to 0.25 pg) and specific radioimmunoassay for this peptide, and we are currently repeating the various observations on this peptide reported in the literature. No AVT has been found until now with this assay, in Wistar rat pituitaries and in brains from day 17 of pregnancy until postnatal day 6, in two midpregnancy sheep pituitaries (kindly donated by Dr. P.W. Nathanielsz) or in human midpregnancy amniotic fluid (Table II). These data make us doubt the importance, and even the existence, of arginine-vasotocin in the fetus. The presence of AVT in the fetal pituitary would also not go together with ideas (cf. Sawyer, 1966; De Wied, 1978) about the molecular evolution of neurohypophysial peptides. If AVT were indeed the 'ancestral peptide' that was changed during phylogeny by amino acid substitution, it is hard to imagine how this mutation process could be repeated in each generation anew during ontogeny.

The physiological role of the fetal neurohypophysial hormones in early pregnancy remains to be determined. Neurohypophysial hormones were reported to have only a very slight effect on urinary concentration in the human newborn (Heller, 1944). This relative insensitiveness to AVP cannot be attributed to a lack of collecting tube responsiveness to the hormone, but rather to the poorly developed osmotic gradient in the renal medulla (Abramov and Dratwa, 1974). Neurohypophysial hormones could also affect water balance of the fetus by acting on the fetal urinary bladder, skin or the extraembryonic membranes (for review see Challis et al., 1976). Perks and Vizsolys (1973) have speculated that the neuro-

TABLE II
NEUROHYPOPHYSIAL HORMONE LEVELS IN MAN (pg/ml) $\pm$ S.E.M.

	<i>Oxytocin</i>	<i>Vasopressin</i>	<i>Vasotocin</i>
Midpregnancy amniotic fluid n = 3	< 4	< 1	< 1
Maternal plasma at term n = 16	20.6 $\pm$ 3.1	< 2	< 2
Maternal plasma immediately postterm n = 5	28.7 $\pm$ 6.2	< 2	< 2
Umbilical cord plasma n = 5	68.1 $\pm$ 18.4	75.8 $\pm$ 50.6	< 2

hypophysial hormones pass via the fetal urine into the amniotic fluid and cause water uptake into the amniotic cavity. Oxytocin, AVP and AVT were not detectable in amniotic fluid at midpregnancy, however (Table II). In addition, the high frequency of hydramnios in anencephalics (Honnebier and Swaab, 1973), together with the absence of the fetal neurohypophysis in the majority of these children (Angevine, 1938), makes it unlikely that this mechanism is of primary importance for the formation of amniotic fluid.

As a possible explanation for hydramnios in anencephaly, a disturbed swallowing of amniotic fluid or an increased fetal urine output because of the observed kidney changes and AVP deficiency have been mentioned (Nakano, 1973; Potter and Craig, 1975), but both possibilities are doubtful (Taussig, 1927; Ferm and Saxon, 1971; Honnebier and Swaab, 1973). Another, perhaps additional, mechanism could be that hydramnios is due to an overproduction of cerebrospinal fluid directly into the amnion (cf. Taussig, 1927), since structures resembling the intact choroid plexus are prominent in anencephaly (Potter and Craig, 1975). In this context it seems of importance that AVP has been demonstrated to be present in the cerebrospinal fluid of adult organisms (Dogterom et al., 1978), while a related peptide was found in the choroid plexus (Rudman and Chawla, 1976). AVP is thought to reduce cerebrospinal fluid production (for references see Brownfield and Kozlowski, 1977). The latter authors described (in adult rat) neurosecretory fibers stained for neurophysins that innervated the choroid plexus. Recently we have shown that such fibers do indeed contain neurohypophysial hormones (Fig. 3).

Although all these data have still to be confirmed in the fetus, hydramnios in anencephaly might thus be due to increased cerebrospinal fluid production directly into the amniotic fluid by the exposed choroid plexus in the absence of vasopressin.

Fig. 3. A neurosecretory fiber (arrows) running into the choroid plexus (CP) of the lateral ventricle (LV) of an adult Wistar rat. The staining was performed by M. Everts using unpurified anti-vasopressin (# 125) 1:800 according to the unlabeled antibody enzyme technique of Sternberger (for details see Buijs et al., 1977). d, dorsal; l, lateral; v, ventral; m, medial; ST, stria terminalis. The horizontal bar indicates 50 μ m.

The fetal brain and the onset of parturition

A wealth of data shows that, in sheep, the fetal hypothalamus is primarily responsible for the sequence of events that results in birth. Since this sequence involves fetal pituitary ACTH, an ACTH releasing factor seems to be *the* hypothalamic stimulus initiating labor (for recent reviews see Liggins et al., 1977b; Nathanielsz et al., 1977). There is some evidence that AVP might be this hypothalamic factor (e.g. Challis and Thorburn, 1976). Intravenous infusion of AVP into the sheep fetus results in increased ACTH release (Jones and Rurak, unpublished observations, mentioned in Challis et al., 1976). A rise in fetal plasma AVP has been reported during the last few days before birth in the lamb (Alexander et al., 1974) but was not confirmed in later studies, in which AVP was found to rise only during the last hours of pregnancy (Stark, 1977). It remains questionable, therefore, whether fetal AVP is indeed of any physiological importance for the initiation of labor in sheep. It is certainly not such a factor in rats since fetal brain aspiration does not prolong gestation length in this species (Swaab et al., 1977a) while homozygous Brattleboro rats with a homozygous litter have even a shorter gestation length than do heterozygous animals (Boer, unpublished observations).

The initiation of labor in man has appeared to be less dependent on the fetal brain and pituitary than in sheep. Data such as increased cortisol levels in the human amniotic fluid and umbilical cord during pregnancy and labor indicated a role of the human fetus in the onset of parturition similar to that of the sheep (Challis and Thorburn, 1976). Yet, in contrary to the general opinion expressed in the literature (e.g. Potter and Craig, 1975), we found the mean gestation length in human anencephalics without hydramnios to be the same as that of the controls. However, a high percentage of both pre- and post-mature labors were found in anencephaly (Honnebier and Swaab, 1973) (Fig. 4 left). A similar distribution of births was found in rhesus monkeys: the majority of the experimental anencephalics delivered either pre- or post-term (Novy, 1977) (Fig. 4 right).

Additional data arguing against a crucial role of the fetal brain in the initiation of labor are the few reported cases of acephaly (cf. Liggins, 1974), pituitary aplasia (cf. Swaab and Honnebier, 1974) and microcephaly, accompanied by absence of the hypothalamus (Janigan et al., 1962) in man, which on the average did not deliver post-term. All these facts show that the fetal pituitary in the primate does not play the same triggering role in the initiation of labor as it does in sheep, but rather is involved in the precision of control of the initiation of labor within close limits around the species mean. It is not known whether the mechanisms by which the brain effectuates this 'timing' mechanism in man is also the fetal hypothalamo-hypophysial-adrenal system which initiates labor in sheep. Arguing in favor of this possibility is the finding that either corticosteroid or ACTH administration in the human fetus initiated labor in postmature pregnancies (Mati et al., 1973; Nwosu et al., 1976), and did not induce labor at term (Gamissans et al., 1975, 1976). Moreover, a tendency towards prolongation of pregnancy length was reported following betamethasone treatment of premature labors (Liggins and Howie, 1972).

The fetal brain and the course of labor

The integrity of the fetal brain appears to be necessary for a normal course of delivery in man and rat. In human anencephalics without hydramnios, expulsion of the fetus took twice as long as in controls, and the average time between birth of the fetus and birth of the placenta was nearly three times longer in the anencephalic group. In addition, in the anencephalics 10% of the placenta had to be removed manually, while the overall mean in the university clinic of Amsterdam was only 2% (Swaab et al., 1977a). In this respect it is of

Fig. 4. The influence of anencephaly on the distribution of birth in man (left) and rhesus monkey (right). Left: frequency distribution of gestation length for a control group ($n = 49,996$) and for spontaneous birth of anencephalic fetuses ($n = 29$) without hydramnios, omitting those who had stillborn fetuses with third degree maceration, fetuses which were given intrauterine injections, twins and those in whom labour was induced, (from Honnebier and Swaab, 1973). Right: frequency distribution of gestation length in a group of 310 rhesus monkeys which produced live-born infants and after experimental anencephaly (based upon Novy, 1977, with permission of the Ciba Foundation). Each arrow indicates the birth of one anencephalic fetus. * = delivered by Caesarean section. Note the huge scatter of anencephalic births and the normal mean in both groups.

interest that in the group of children who died during pregnancy (1968–1972: $n = 143$), a high number of placentas (8.4%) had to be removed manually (Huidekoper and Kloosterman, personal communication). All these data point to an active involvement of the fetus in the course of its own delivery, and in the delivery of its placenta.

In the rat a protracted course of labor was found after brain aspiration (Swaab et al., 1977a). Since a prolonged course of labor was also found in Brattleboro rats as compared to normal Wistars, the fetal neurohypophysis may play a role in the acceleration of the course of labor (Swaab et al., 1977a). Such a role of fetal oxytocin was already suspected in 1938 by Bell and Robson, who found appreciable amounts of oxytocin in fetal pig and sheep pituitaries. This possibility is reinforced by the finding that uterine contractions could effectively be evoked in sheep (Nathanielsz et al., 1973) and in man (Honnebier et al., 1974) by injection of posterior lobe hormones into the fetal compartment, despite the conceptual difficulties in postulating the route which the fetal hormones should take to the myometrium (cf. Liggins et al., 1977a). Furthermore, fetal rat pituitary extracts had the potency to induce uterine contractions (Swaab and Boer, 1978). In addition, high levels of these hormones are present in umbilical cord blood (Chard et al., 1977 and Table II) that rise during the last hours of pregnancy in man (Chard et al., 1977) and in sheep (Forsling et al., 1975; Stark, 1977). The fetus thus appears to have the means to stimulate the uterus and, so, the course of labor by increasing its neurohypophysial hormone release.

AVT was found to be oxytocic in the rat at term (Swaab et al., 1977a). Whether this hormone (if indeed present) or related peptides play a role in the acceleration of the course of labor from the fetal side, is the subject of current investigations.

SUMMARY AND CONCLUSIONS

The fetal hypothalamus is active in stimulating intrauterine growth. In man this appears from the low birth weight found in congenital anomalies in which the fetal hypothalamus was absent, i.e. acephaly, anencephaly and certain cases of microcephaly. In rat, fetal growth was impaired after removal of the fetal pituitary and/or brain, or destruction of the hypothalamus. The intermediate lobe hormone, α -MSH, was found to stimulate fetal growth in rat. Although this hormone was also found to be present in the human fetus during the intrauterine growth spurt while absent in human anencephalics, its relation to intrauterine growth has still to be confirmed.

The fetal brain in man is not involved in the initiation of labor in the same way as found in the sheep, but rather plays a role in the exact timing of the moment of birth around the species mean pregnancy length. Neurohypophysial hormones are present in very high concentrations in umbilical blood, and these fetal hormones are thought to accelerate the course of labor. This hypothesis is supported by the protracted course of labor found in human anencephalics, and brainless rat fetuses. The fetus itself plays thus an active role in its own intrauterine growth and parturition by means of neuroendocrine mechanisms.

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REFERENCES

- Abramow, M. and Dratwa, M. (1974) Effect of vasopressin on the isolated human collecting duct, *Nature (Lond.)*, 250: 492–493.
- Alberman, E. (1976) Factors influencing perinatal wastage. In *Fetal Physiology and Medicine*, R.W. Beard and P.W. Nathanielsz (Eds.), Saunders, London, pp. 415–432.
- Alexander, D.P., Bashore, R.A., Britton, H.G. and Forsling, L. (1974) Maternal and fetal arginine vasopressin in the chronically catheterized sheep, *Biol. Neonate*, 25: 242–248.
- Angevine, D.M. (1938) Pathologic anatomy of hypophysis and adrenals in anencephaly, *Arch. Pathol.*, 26: 507–518.
- Bearn, J.G. (1971) The role of the foetal pituitary in organogenesis. In *Hormones in Development*, M. Hamburg and E.J.W. Barrington (Eds.), Appleton-Century-Crofts, New York, pp. 121–134.
- Bell, G.H. and Robson, J.M. (1938) The oxytocin content of the foetal pituitary, *Quart. J. exp. Physiol.*, 27: 205–208.
- Brownfield, M.S. and Kozlowski, G.P. (1977) The hypothalamo-choroidal tract. I. Immunohistochemical demonstration of neurophysin pathways to telencephalic choroid plexuses and cerebrospinal fluid, *Cell Tiss. Res.*, 178: 111–127.
- Buijs, R.M., Swaab, D.F., Dogterom, J. and Van Leeuwen, F.W. (1977) Intra- and extrahypothalamic vasopressin and oxytocin pathways in the rat, *Cell Tiss. Res.*, 186: 423–433 (1978)
- Case, J.F. (1952) Adrenal cortical-anterior pituitary relationships during embryonic life, *Ann. N.Y. Acad. Sci.*, 55: 147–158.

- Challis, J.R.G. and Thorburn, G.D. (1976) The fetal pituitary-adrenal axis and its functional interactions with the neurohypophysis. In *Fetal Physiology and Medicine*, R.W. Beard and P.W. Nathanielsz (Eds.), Saunders, London, pp. 233–250.
- Challis, J.R.G., Robinson, J.S., Rurak, D.W. and Thornburn, G.D. (1976) The development of endocrine function in the human fetus. In *The Biology of Human Fetal Growth*, D.F. Roberts and A.M. Thomson (Eds.), Taylor and Francis, London, pp. 149–194.
- Chard, T., Silman, R.E. and Rees, R.H. (1977) The fetal hypothalamus and posterior pituitary in the initiation of labour. In *The Fetus and Birth, Ciba Foundation Symp. No. 47*, J. Knight and M. O'Connor (Eds.), Elsevier, Amsterdam, pp. 359–378.
- Corner, M.A., Bakhuis, W.L. and Van Wingerden, C. (1973) Sleep and wakefulness during early life in the domestic chicken, and their relationship to hatching and embryonic motility. In *Studies on the Development of Behavior and the Nervous System, Vol. 1. Behavioral Embryology*, G. Gottlieb (Ed.), Academic Press, New York, pp. 245–279.
- De Wied, D. (1978) The modulation of memory processes by vasotocin, the evolutionary oldest neuro-secretory principle, this volume.
- Dicker, S.E. and Tyler, C. (1953) Vasopressor and oxytocic activities of the pituitary glands of rats, guinea pigs and cats and of human foetuses, *J. Physiol. (Lond.)*, 121: 206–214.
- Dogterom, J., Van Wimersma Greidanus, Tj.B. and Swaab, D.F. (1978) Evidence for the release of vasopressin and oxytocin into cerebrospinal fluid: measurements in plasma and CSF of intact and hypophysectomized rats, *Neuroendocrinology*, 24: 108–118 (1977).
- Ferm, V.H. and Saxon, A. (1971) Amniotic fluid volume in experimentally induced renal agenesis and anencephaly, *Experientia (Basel)*, 27: 1066–1068.
- Forsling, M.L. (1973) In *Endocrine Factors in Labour, Mem. Soc. Endocrinology No. 20*, A. Klopfer and J. Gardner (Eds.), Cambridge University Press, London, p. 174 (figure).
- Forsling, M.L., Jack, P.M.B. and Nathanielsz, P.W. (1975) Plasma oxytocin concentrations in the foetal sheep, *Horm. Metab. Res.*, 7: 197.
- Fujita, T., Eguchi, Y., Morikawa, Y. and Hashimoto, Y. (1970) Hypothalamic-hypophysial adrenal and thyroid systems: observations in fetal rats subjected to hypothalamic destruction, brain compression and hypervitaminosis A, *Anat. Rec.*, 166: 659–672.
- Galabov, P. and Schiebler, T.M. (1978) On the development of the principles in the neural lobe of the rat. In *Neural Hormones and Reproduction*, D.E. Scott, G.P. Koslowski and A. Weindl (Eds.), Karger, Basel, pp. 57–66.
- Gamissans, O., Pujol-Amat, P., Davi, E., Pérez-Picanol, E. and Wilson, G.R. (1975) The effect of intra-amniotic administration of β -metasone on the onset of labour in human pregnancy, *Acta endocr. (Kbh.)*, Suppl. 199: 95.
- Gamissans, O., Davi, E., Pérez-Picanol, E., Pujol-Amat, P. and Wilson, G.R. (1976) Effect of ACTH administration into the fetus, on onset of labour and on maternal plasma steroid levels. In *Research on Steroids, Vol. 7*, A. Vermeulen (Ed.), Elsevier/North-Holland Biomedical Press, Amsterdam.
- Heller, H. (1944) The renal function of newborn infants, *J. Physiol. (Lond.)*, 102: 429–440.
- Heller, H. and Pickering, B.T. (1960) Identification of a new neurohypophysial hormone, *J. Physiol. (Lond.)*, 152: 56P–57P.
- Honnebier, W.J. and Swaab, D.F. (1973) The influence of anencephaly upon intrauterine growth of fetus and placenta and upon gestation length, *J. Obstet. Gynaecol.* 80: 577–588.
- Honnebier, W.J. and Swaab, D.F. (1974) Influence of α -melanocyte-stimulating hormone (α -MSH), growth hormone (GH) and fetal brain extracts on intrauterine growth of fetus and placenta in the rat, *J. Obstet. Gynaecol.*, 81: 439–447.
- Honnebier, W.J. and Swaab, D.F. (1975) Regulation of growth velocity by the foetus, *Acta endocr. (Kbh.)*, Suppl. 199: 97.
- Honnebier, W.J., Jöbsis, A.C. and Swaab, D.F. (1974) The effect of hypophysial hormones and human chorionic gonadotrophin (HCG) on the anencephalic fetal adrenal cortex and on parturition in the human, *J. Obstet. Gynaecol.*, 81: 423–438.
- Janigan, D.T., Smith, O.D. and Nichols, J. (1962) Observations on the central nervous system, pituitary and adrenal in two cases of microcephaly, *J. clin. Endocr. Metab.*, 22: 683–687.
- Jost, A. (1954) Hormonal factors in the development of the fetus, *Cold Spr. Harb. Symp. quant. Biol.*, 19: 167–181.
- Kastin, A.J., Miller, L.H., Nockton, R., Sandman, C.A., Schally, A.V. and Stratton, L.O. (1973)

- Behavioral aspects of melanocyte-stimulating hormone (MSH). In *Drug Effects on Neuroendocrine Regulation, Progress in Brain Research, Vol. 39*, E. Zimmerman, W.H. Gispen, B.H. Marks and D. de Wied (Eds.), Elsevier, Amsterdam, pp. 461–470.
- Kittinger, G.W. (1977) The endocrine regulation of fetal development and its relation to parturition in the rhesus monkey. In *The Fetus and Birth, Ciba Foundation Symp. No. 47*, J. Knight and M. O'Connor (Eds.), Elsevier, Amsterdam, pp. 235–257.
- Lewis, P.D., Patel, A.J., Béndek, G. and Balázs, R. (1977) Do drugs acting on the nervous system affect cell proliferation in the developing brain?, *Lancet*, 1: 399–401.
- Liggins, G.C. (1974) The influence of the fetal hypothalamus and pituitary on growth. In *Size at Birth, Ciba Foundation Symp. No. 27*, K. Elliott and J. Knight (Eds.), Elsevier, Amsterdam, pp. 165–183.
- Liggins, G.C. and Howie, R.N. (1972) A controlled trial of antepartum glucocorticoid treatment for prevention of the respiratory distress syndrome in premature infants, *Pediatrics*, 50: 515–525.
- Liggins, G.C., Forster, C.S., Grieves, S.A. and Schwartz, A.L. (1977a) Control of parturition in man, *Biol. Reprod.*, 16: 39–56.
- Liggins, G.C., Fairclough, R.J., Grieves, S.A., Forster, C.S. and Knox, B.S. (1977b) Parturition in the sheep. In *The Fetus and Birth, Ciba Foundation Symp. No. 47*, J. Knight and M. O'Connor (Eds.), Elsevier, Amsterdam, pp. 5–30.
- Mati, J.K.G., Horrobin, D.F. and Bramley, P.S. (1973) Induction of labour in sheep and humans by single doses of corticosteroids, *Brit. med. J.*, 2: 149–151.
- Nakano, K.K. (1973) Anencephaly: a review, *Develop. Med. Child Neurol.*, 15: 383–400.
- Nathanielsz, P.W., Comline, R.S. and Silver, M. (1973) Uterine activity following intravenous administration of oxytocin to the foetal sheep, *Nature (Lond.)*, 243: 471–472.
- Nathanielsz, P.W., Jack, P.M.B., Krane, E.J., Thomas, A.L., Ratter, S. and Rees, L.H. (1977) The role and regulation of corticotropin in the fetal sheep. In *The Fetus and Birth, Ciba Foundation Symp. No. 47*, J. Knight and M. O'Connor (Eds.), Elsevier, Amsterdam, pp. 73–98.
- Novy, M.J. (1977) Endocrine and pharmacological factors which modify the onset of labour in rhesus monkeys. In *The Fetus and Birth, Ciba Foundation Symp. No. 47*, J. Knight and M. O'Connor (Eds.), Elsevier, Amsterdam, pp. 259–295.
- Nwosu, U.C., Wallach, E.E. and Bolognese, R.J. (1976) Initiation of labor by intra-amniotic cortisol instillation in prolonged pregnancy, *Obstet. Gynecol.*, 47: 137–142.
- Oliver, C., Barnea, A., Warberg, J., Eskay, R.L. and Porter, J.C. (1977) Distribution, characterization, and subcellular localization of MSH in the brain. In *Melanocyte Stimulating Hormone: Control, Chemistry and Effects*, F.J.H. Tilders, D.F. Swaab and Tj.B. Van Wimersma Greidanus (Eds.), Karger, Basel, pp. 162–166.
- Paull, W.K. (1973) *A Light and Electronmicroscopic Study of the Development of the Neurohypophysis of the Fetal Rat*, Doctoral dissertation, Univ. South. California, U.S.A.
- Perks, A.M. and Vizsolyi, E. (1973) Studies of the neurohypophysis in foetal mammals. In *Foetal and Neonatal Physiology, Proc. Sir Joseph Barcroft Centenary Symposium*, K.S. Comline, K.W. Cross, G.S. Dawes and P.W. Nathanielsz (Eds.), Cambridge University Press, London, pp. 430–438.
- Potter, E.L. and Craig, J.M. (1975) *Pathology of the Fetus and the Infant*, Yearbook Medical Publishers, Chicago.
- Querido, A., Bleichrodt, N. and Djokomoeljanto, R. (1978) Thyroid hormones and human mental development, this volume.
- Rieutort, M. and Jost, A. (1976) Growth hormone in encephalotomized rat fetuses, with comments on the effect of anesthetics, *Endocrinology*, 98, 1123–1129.
- Roberts, D.F. and Thomson, A.M. (1976) (Eds.) *The Biology of Human Fetal Growth, Symposia Society for the Study of Human Biology, Vol. 15*. Taylor and Francis, London.
- Rudman, D. and Chawla, R.K. (1976) Antidiuretic peptide in mammalian choroid plexus, *Amer. J. Physiol.*, 230: 50–55.
- Rudman, D., Scott, J.W., Del Rio, A.E., Houser, D.H. and Sheen, S. (1974) Melanotropic activity in regions of rodent brain, *Amer. J. Physiol.*, 226: 682–686.
- Sawyer, W.H. (1966) Biological assays for neurohypophysial principles in tissues and in blood. In *The Pituitary Gland, Vol. 3*, G.W. Harris and B.T. Donovan (Eds.), Butterworths, London, pp. 288–329.
- Silman, R.E., Chard, T., Lowry, P.J., Smith, I. and Young, I.M. (1976) Human foetal pituitary peptides and parturition, *Nature (Lond.)*, 260: 716–718.

- Skowsky, R. and Fisher, D.A. (1973) Immunoreactive arginine vasopressin (AVP) and arginine vasotocin (AVT) in the fetal pituitary of man and sheep, *Clin. Res.*, 21: 205.
- Sohal, G.S. (1976) Effects of reciprocal forebrain transplantation on motility and hatching in chick and duck embryos, *Brain Res.*, 113: 35–43.
- Stark, R. (1977) In *The Fetus and Birth, Ciba Foundation Symp. No. 47*, J. Knight and M. O'Connor (Eds.), Elsevier, Amsterdam, discussion p. 371.
- Swaab, D.F. and Boer, K. (1977) The role of the fetal brain and pituitary in intrauterine growth and parturition. In *Proc. Vth Int. Symp. Obstet. Gynaecol.*, Barcelona, in press.
- Swaab, D.F. and Honnebier, W.J. (1973) The influence of removal of the fetal rat brain upon intrauterine growth of the fetus and the placenta and on gestation length, *J. Obstet. Gynaecol.*, 80: 589–597.
- Swaab, D.F. and Honnebier, W.J. (1974) The role of the fetal hypothalamus in development of the fetoplacental unit and in parturition. In *Integrative Hypothalamic Activity, Progress in Brain Research, Vol. 41*, D.F. Swaab and J.P. Schadé (Eds.), Elsevier, Amsterdam, pp. 255–280.
- Swaab, D.F. and Pool, C.W. (1975) Specificity of oxytocin and vasopressin immunofluorescence, *J. Endocr.* 66: 263–272.
- Swaab, D.F. and Visser, M. (1977) A function for α -MSH in fetal development and the presence of an α -MSH-like compound in nervous tissue. In *Melanocyte Stimulating Hormone: Control, Chemistry and Effects*, F.J.H. Tilders, D.F. Swaab and Tj.B. Van Wimersma Greidanus (Eds.), Karger, Basel, pp. 170–178.
- Swaab, D.F., Nijveldt, F. and Pool, C.W. (1975) Distribution of oxytocin and vasopressin in the rat supraoptic and paraventricular nucleus, *J. Endocr.*, 67: 461–462.
- Swaab, D.F., Visser, M. and Tilders, F.J.H. (1976) Stimulation of intrauterine growth by α -MSH, *J. Endocr.* 70: 445–455.
- Swaab, D.F., Boer, K. and Honnebier, W.J. (1977a) The influence of the fetal hypothalamus and pituitary on the onset and course of parturition. In *The Fetus and Birth, Ciba Foundation Symp. No. 47*, J. Knight and M. O'Connor (Eds.), Elsevier, Amsterdam, pp. 379–400.
- Swaab, D.F., Van Leeuwen, F.W., Dogterom, J. and Honnebier, W.J. (1977b) The fetal hypothalamus and pituitary during growth and differentiation, *J. Steroid Biochem.*, 8: 545–551.
- Swaab, D.F., Visser, M. and Boer, G.J. (1978) The fetal brain and intrauterine growth. In *Proc. Fifth Unigate Paediatric Workshop: Paediatrics and Growth, Symposium Paediatrics and Growth, London, 1977*, D. Barltrop (Ed.), in press.
- Taussig, F.J. (1927) The amniotic fluid and its quantitative variability., *Amer. J. Obstet. Gynecol.*, 14: 505–517.
- Thommes, R.C., Hajek, A.S. and McWhinnie, D.J. (1973) The influence of 'hypophysectomy' by means of surgical decapitation on skeletal growth in the developing chick embryo, *J. Embryol. exp. Morph.*, 29: 503–513.
- Van de Poll, N.E., De Bruin, J.P.C., Van Dis, H. and Van Oyen, H. (1978) Sex hormones in behavioral development, this volume.
- Van Wimersma Greidanus, Tj.B. (1977) Effects of MSH and related peptides on avoidance behavior in rats. In *Melanocyte Stimulating Hormone: Control, Chemistry and Effects*, F.J.H. Tilders, D.F. Swaab and Tj.B. Van Wimersma Greidanus (Eds.), Karger, Basel, pp. 129–139.
- Vaudry, H., Oliver, C., Vaillant, R. and Kraicer, J. (1976) Bioactive and immunoreactive α MSH in the rat brain. In *Proc. Vth Int. Congr. Endocr.*, Hamburg, Abstract No. 667.
- Vaudry, H., Vaillant, R., Trochard, M.C. and Kraicer, J. (1977) MSH-like peptides in the brain of hypophysectomized rats. In *Proc. XXVIIth Int. Congr. Physiol. Sci.*, Paris, Abstract p. 781.
- Visser, M. and Swaab, D.F. (1977) α -MSH in the human pituitary. In *Melanocyte Stimulating Hormone: Control, Chemistry and Effects*, F.J.H. Tilders, D.F. Swaab and Tj.B. Van Wimersma Greidanus (Eds.), Karger, Basel, pp. 42–45.
- Vizsolyi, E. and Perks, A.M. (1976) Neurohypophysial hormones in fetal life and pregnancy. II. Chromatographic studies in the sheep (*Ovis aries*), *Gen. comp. Endocr.*, 29: 41–50.
- Winick, M. (1976) (Ed.) *Malnutrition and Brain Development*, Oxford University Press, New York.