Life Sciences, Vol. 41, pp. 2589-2596
Printed in the U.S.A.

Pergamon Journals

MINIREVIEW

MORPHOLOGICAL AND BIOCHEMICAL CHANGES IN THE PINEAL GLAND IN PREGNANCY

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Summary

Although systematic and detailed studies of pineal structure and function during pregnancy are rare, the available evidence indicates that morphological and biochemical changes do take place in this gland during this reproductive state. The majority of studies indicate increased activity in cytoplasmic organelles and enzymes of pinealocytes during gestation. Changes in pineal and plasma melatonin levels in pregnancy have been described in a number of species. Results of biochemical studies emphasize the existence of the feedback system which involves the gonads, the hypothalamus and the pineal gland. More ultrastructural and biochemical studies on this intriguing gland in pregnancy are fully warranted.

Much information is available concerning the relationship between the pineal gland and the gonad, the effects of the pineal on the estrous cycle and ovulation, and the effects of pinealectomy or pineal extracts on reproduction and pregnancy in mammals (1,2). The evidence indicates that the pineal gland may exert its influence at all levels of the neuroendocrine-reproductive hierarchy (2,3). However, systematic and detailed studies of pineal structure and function during pregnancy are rare.

Morphological and Histochemical Changes

Over fifty years ago some authors attempted to determine whether any relationship exists between the pineal gland and pregnancy. Some differences in the shape of the pineal gland in women due to the number of pregnancies were reported (4). A comparative study was made of the function of the gland during pregnancy and its activity in non-pregnant women (5). Pineal concretions were found in a much higher percentage of women who were or had been pregnant, than in women who had never been pregnant. The concretions were reported to increase with each pregnancy. During pregnancy the bitch pineal gland underwent physiological involution (6) which became more noticeable during parturition and puerperium. Data have been presented which emphasized the morphological variations of the pineal gland of sheep, cattle and rats in relation to the physiological condition of the reproductive organs (7). This investigation consisted of

0024-3205/87 $3.00 + .00

a study of 153 pineal glands from sheep, 110 from cattle and 755 from rats. The pineal gland in pregnant sheep presented evidence of increased function when compared with that in nonpregnant ewes as it showed increased vascularity, perivascular lymph spaces, and increased size and weight. The largest glands were observed in ewes whose ovaries exhibited well-developed ovarian follicles.

Pregnancy was observed to exert an effect on the rodent pineal as evidenced by a decrease in pineal weight with ten or more fetuses (table 1) (8). Pineal glands of pregnant guinea-pigs showed signs of increased activity in the second half of gestation as revealed by enzyme histochemistry (9). Report was made of a strong increase of NADH diaphorase and NADPH diaphorase activities both of which share in oxidation of pyruvate to acetyl-CoA, in the second half of pregnancy. This increase disappeared after delivery, oophorectomy or hysterectomy.

TABLE I

Weight of the Pineal Gland and Nucleolar Area of Pinealocytes in Pregnancy

Condition	No. of rats	Mean Pineal Weight in mg	Mean Nucleolar Size of Pinealocytes (Cross-sectional Area in um^2)
Non-pregnant control	25	1.32	1.38
10th to 20th day pregnant:			
Less than 10 fetuses	10	1.25	2.09* (on day 20; n = 28; no. of fetuses unknown)
Ten or more fetuses	16	1.07*	

*Significantly different from control (P<0.01)

(Table adapted from Huang and Everitt, 1965 and Satodate *et al.*, 1980).

Rzeszowska-Tokarska (10) made histochemical observations on hydrolytic enzymes' activities in the rodent pineal gland in different periods of pregnancy. She reported that glucose-6-phosphate, alkaline phosphatase, ATPase, and thiamine pyrophosphatase activities were enhanced in the second half of pregnancy in the rat.

Various authors have described cellular changes which indicate a more metabolically active pineal gland in pregnancy. Lues (11) described an increased number of "dark" cells with more mitochondria, smooth endoplasmic reticula and agranular vesicles in the second half of gestation, and reversion of this change to normal within a week after delivery. Vollrath and Huss (12) studied "synaptic" ribbons (vesicle-crowned rodlets) in the rat in pregnancy and other experimental conditions. They concluded that they were true organelles possibly involved in coupling adjacent pinealocytes functionally. Synaptic ribbons were found to be numerous in the pineal glands of the pregnant and sterile female guinea-pigs (13). However they were scarce and difficult to locate in tissue from the fertile, non-pregnant females and from the reproductively active males. The evidence presented here lends credence to the possibility that this structure may serve a sensory or receptor function in the guinea pig pineal gland. An increase in the number of lysosomes and an increase in the Golgi apparatus were noted in pregnant rats (14). In addition the author described a distinct peak in hydroxyindole-o-methyl transferase activity at day 15 of pregnancy, followed by a decrease from days 20 to 22.

Karasek et al., (15) observed significant changes in the numbers of Golgi profiles (GP) and dense-core vesicles (DCV) in the last two days of pregnancy when the mean numbers of GP and DCV per 1,470 um^2 were 25.65 and 85.5 respectively, when compared to 16.83 and 39.66, the means for the previous three days. The number of vacuoles containing a flocculent material (VFC) was significantly lower at day 22, down from day 21 ($P<0.05$) and from days 18-20 of pregnancy ($P<0.01$); the number of lysosomes also increased almost two-fold at day 22 and differed significantly from the previous four days ($P<0.01$). The number of lipid droplets showed a slight, non-significant increase by day 21 and was significantly different at day 22 from the previous four days ($P<0.01$). The last day of gestation is the period in which the most dramatic changes in LH and prolactin levels occurred. The evidence suggested that the pineal gland may play a subtle role in pregnancy.

In studies on the mole Pevet and Smith (16) noted an increase in the quantity of Golgi apparatuses and paracrystalline structures during estrus, gestation and lactation in female pinealocytes, the increase being larger during gestation and lactation than during estrus. The evidence seemed to demonstrate a close relationship between the endocrine activity of the hypophyseal-gonadal axis and the synthesis of some compounds by the pinealocytes.

Satodate et al. (17) made an electron microscopical morphometrical study of pinealocytes of pregnant rats. The cross-sectional area of the nucleoli was found to be larger in the pinealocytes of rats in pregnancy and early puerperium (Table 1). Their evidence suggested that pineal function is enhanced in pregnancy, a period during which gonadal function is also elevated.

Nesic and Kadic (18) in a morphodynamic investigation of the ewe pineal gland during pregnancy showed that clear changes occurred in nuclear volumes of pinealocytes. They concluded that the increase in nuclear volumes during the final period of pregnancy with hypertrophy and hyperemia resulted from an increase of function as a response of the gland to increased concentration of estrogen. In agreement with the results of Nesic and Kadic (18) are those of Petrusevska and Koceva-Danilova (19) who reported on the hypertrophy of pinealocytes during the second half of pregnancy in epiphyses of mice.

Biochemical Changes

Changes in pineal and plasma melatonin levels in pregnancy have been described in a number of species. The concentration of melatonin in maternal peripheral plasma was measured during late pregnancy, term and pre-term labor (Mitchell *et al.*, 1979). All samples were collected between 0800 and 2230 hours. When compared to levels in late pregnancy, the mean levels of melatonin in peripheral plasma were higher during both term and pre-term labor; this difference was statistically significant only in labor at term. Umbilical arterial and venous blood samples were taken after spontaneous vaginal delivery at term and at elective Caesarean section also at term. Umbilical plasma concentrations of melatonin were significantly greater than maternal peripheral plasma concentrations during labor. For both groups of umbilical samples a significant arterio-venous difference was demonstrated with elevated venous levels after spontaneous vaginal delivery but higher arterial levels at Caesarean section.

Pang *et al.*, (21) reported on changes in plasma concentrations of melatonin during pregnancy in humans. Blood samples were collected by venipuncture from Chinese females (age 18-39) between 1000 - 1230 h, during 1-12, 12-18, 18-24, 24-30, 30-36 and 36-42 weeks of normal pregnancy and 1-5 minutes after normal delivery. Plasma melatonin was high in weeks 1-24, low in weeks 24-36, and then high again in weeks 36-42 (fig. 1). After parturition, levels of melatonin and the steroids, estrogen and progesterone, dropped precipitously, but those of protein hormones, HCG, FSH and LH, remained unchanged in the maternal circulation. Their findings suggested that, during gestation, estradiol and progesterone may inhibit, but FSH may facilitate the secretion of pineal melatonin.

Fluctuations of pineal melatonin content in rats during different stages of pregnancy (fig. 1) have also been demonstrated (22). High pineal melatonin contents from about 36 h after mating were followed by generally lower levels in later periods of pregnancy. The higher levels of pineal melatonin at mid-light and mid-dark during the early period of pregnancy suggested an increase in the synthesis and secretion of pineal melatonin. Devecerski (23) described decreased activities of enzymes involved in glycolysis in the rodent pineal gland on day 15 of pregnancy.

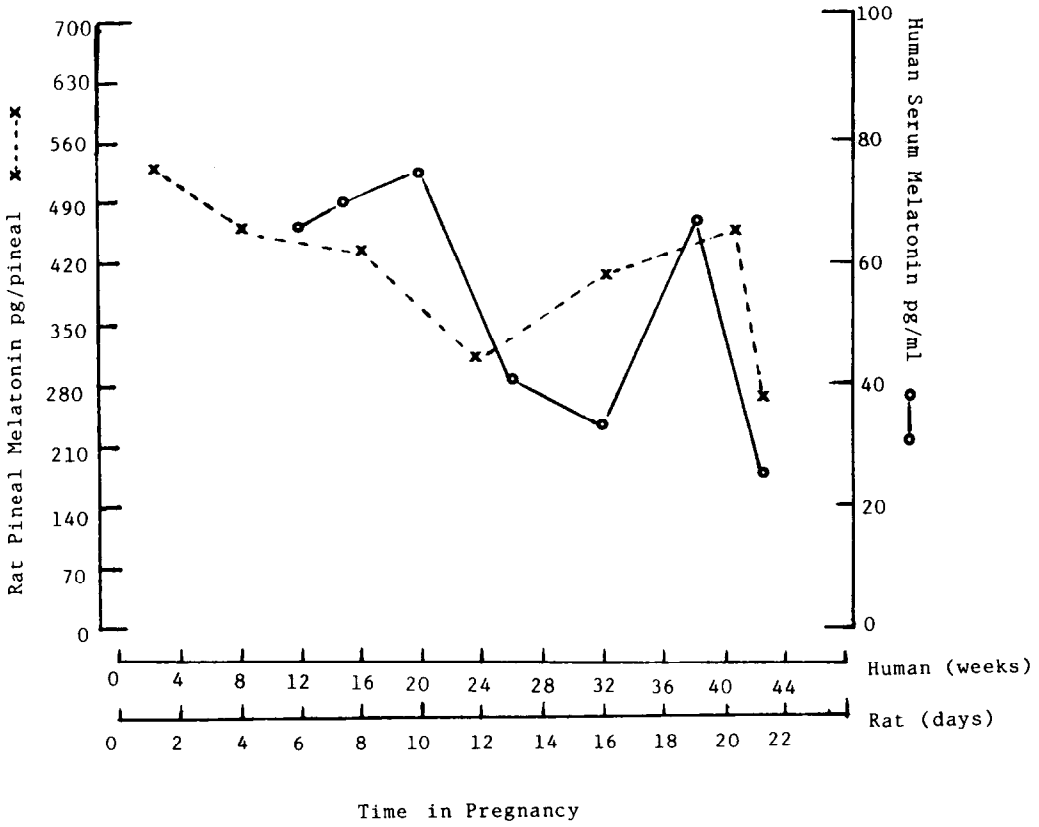

FIG. 1

Comparison between human plasma melatonin and rodent pineal melatonin during pregnancy. (Modified from Pang *et al.*, 1985.)

In pregnant or pseudopregnant mink (*Mustela vison*) maintained under different photoperiods, Ravault *et al.*, (24) described diurnal variations of plasma melatonin concentrations. Studies on the fetal sheep pineal revealed that hydroxyindole-O-methyltransferase (HIOMT) activity was detectable during the last trimester of pregnancy increasing dramatically in the 5-6 days before birth (25), coincident with increased glandular melatonin content (26). Pineal gland changes in HIOMT and MAO (monoamine oxidase) activities during the period of blastocyst activation also take place in the tammar wallaby, *Macropus eugenii* (27). Pseudopregnant rats were reported to have a different diurnal

pattern of HIOMT activity although no deviation in its mean rate (28).

Nir and Hirschmann (29) believe that the pineal may play the role of moderator between abnormal environmental or physiological conditions and the functions of hormones in gestation; its role in pregnancy may become more obvious if animals are exposed to conditions which drastically affect their endocrine system. Nir et al. (30) have suggested that during the last phase of pregnancy in the rat the pineal gland may play a role in the modification of gonadotrophin synthesis and release. The evidence indicates that the pineal affects LH release and PRL synthesis and probably PRL release as well.

Melatonin implants into pregnant rats throughout the entire period of gestation significantly lowered the prenatal serum and pituitary level of LH and enhanced the prolactin level in serum, while diminishing it in the pituitary (31). Neither the abrupt physiological decline of serum progesterone nor the enhanced level of estrogen present during the period preceding delivery seemed to be affected by melatonin. The results suggested that melatonin exerts its inhibitory action on hypothalamic luliberin and prolactostatin not by utilizing an additional antigonadotrophic pineal factor and not by the steroid sex hormones.

Other findings of these same authors (32) indicated that darkness-induced endocrine changes in rat dams during the perinatal period were not mediated by the pineal gland. Serum and pituitary LH, prolactin and progesterone changes recorded in parturient rats exposed to continuous darkness throughout pregnancy were not prevented by early ablation of the pineal gland.

Conclusions

Thus it is seen that morphological and biochemical changes in pinealocytes reflect the reproductive condition of the animal. However, more ultrastructural and biochemical studies need to be carried out on this gland during pregnancy. In addition to the pineal indoleamines such as melatonin, peptides, polypeptides and proteins such as LHRH, TRH and somatostatin also seem to be involved in this gland's endocrine activities (33,34,35,36,37). However, no studies have been carried out on changes in the latter group of compounds in the pineal during pregnancy.

Pregnancy as well as the estrous cycle, castration and the administration of gonadotrophins or gonadal steroids affect pinealocyte structure and biochemistry (38,39,40,41,42). The evidence also indicates a feedback system which involves the gonads and the pineal gland. Secretions from the pineal gland share in the control of reproductive function. In turn gonadal steroids, gonadotrophins and prolactin modify pineal metabolic activity and affect the rate of synthesis of pineal hormones (3). There is now well-confirmed evidence for melatonin and estrogen receptors in the pineal as well as in the hypothalamus. Although there is clear evidence of a number of different methoxyindoles

being secreted by the pineal, with marked species differences among mammals, the molecular identity of many of these so-called "hormonal" peptides described in pineal tissue remains questionable and their function within the pineal is still enigmatic (36).

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