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Impacts of Photoperiod and Maternal Pineal Gland on Pre- and Post-natal development of Indian palm Squirrel *F. pennanti*

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Abstract:
Studies till date suggest the existence of a fetal biological clock in suprachiasmatic nuclei entrained by the circadian signal from mother. Melatonin from maternal pineal gland reaches to the fetus by crossing every biological barrier including placenta, hence fetuses were exposed to similar melatonin variation as their mother. Experimental modulations of maternal pineal gland activity of pregnant females either by exposing the them to different photoperiodic schedules or by exogenous melatonin treatments till the date of parturition, regulated the fetal plasma level of melatonin, thereby the prenatal (fetal) growth and development. This clearly suggests the maternal transport of melatonin to their fetus through placenta since fetal retino-hypothalamic tract was incomplete. An extension of experimental schedules till 60 days of post-partum period regulated the neonatal pineal gland activity and gonadal maturation along with their plasma levels of melatonin and sex steroids suggesting clearly the phenomenon of maternal transfer of melatonin to their young ones during the post-natal period, when the neonates were solely dependent on the mother's milk for their nutrition and energetic demands. On the basis of above observations we may suggest that the maternal pineal gland activity regulate the prenatal development by passing its melatonin to fetus via placenta and post-natal growth and sexual maturation by passing maternal melatonin to neonates via milk. Hence, the photoperiod perceived by mother is translated into the maternal plasma level of melatonin which not only regulates the prenatal but also the post-natal growth and sexual maturation of neonates.

Key words: Pineal, melatonin, photoperiod, maternal, pre-natal, post-natal, gestation

Introduction:

The pineal gland is known to have a widely accepted role in seasonal changes of gonadal physiology and hence the reproduction of several seasonally breeding mammalian species. The seasonality in reproduction is usually enforced by a dependence on day length (photoperiod). The information about the daily photoperiod passes form the retina to the suprachiasmatic nucleus (SCN) and the superior cervical ganglion (SCG) to the pineal gland, where the melatonin is secreted at a higher rate at night [1]. The daily duration of the increase in melatonin secretion regulates the secretion of gonadotropins [2] and gonadal steroids, which regulates the breeding activity of seasonally breeding mammals. It has been claimed that during long photoperiod, animals are physiologically pinealectomised [3] and during short photoperiods the pineal is highly active. Hence, due to the seasonal changes in photoperiod, the pineal gland regulates the seasonality of reproduction in several mammalian species. Pineal-gonadal function has been extensively studied in male mammals. However, reports are lacking to explain the photoperiodic-pineal-gonadal response in the seasonally breeding female that too during the most important phase of female reproductive cycle i.e. gestation.

After successful mating, fertilization of ovum with sperm occurs and finally the uterine wall is being implanted with embryos. Prolonged maternal care during embryonic and neonatal period enhances the chance of survival of offspring. Estrogen and especially progesterone prepare maternal body for successful internal fertilization and hospitable acceptance of the embryo. There are some indications suggesting pineal implication in processes connected with gestation and fertility [4,5]. Recently Bishnupuri and Haldar reported the ultramorphometric analyses of pineal organ from pregnant Indian palm squirrel *F. pennanti* [6].

Maternal-fetal pineal gland and photoperiod:

Mother plays a key role in sheltering the fetuses from the external environment. In this context, it seems remarkable that the mother is also actively involved in transferring environmental information to the fetus. During gestation, the mother generates signals, which allow the fetus to perceive the length of the light portion of the dark-light cycle. We refer to these two different forms of prenatal communication as maternal-fetal communication of day-length and maternal-fetal communication of circadian phase respectively.

Studies in several mammalian species show that

during fetal life, a biological clock in suprachiasmatic nuclei (SCN) is oscillating in phase (time) with environmental light-dark cycle and this fetal clock is entrained by circadian signals from mother. Light induced neural signals are conveyed to SCN by mother's retino-hypothalamic pathway (RHP), entraining her circadian rhythm. Maternal output signals then entrain the fetal clock at a time when the innervation of fetal SCN by RHP is incomplete.

However, till date, no information is available whether the pineal gland influences fetal development of any mammalian species. How information about the environments (photoperiod, temperature, humidity etc.) and others (hormonal or metabolic) are transferred from mother to their young ones is yet not clear. Only finger countable reports are available suggesting the phenomenon of maternal transfer of photic information to her young ones via the pineal gland.

Some recent studies suggested the phenomenon of maternal transfer of photoperiodic information to young ones via pineal gland [7]. Horton et al. and Stetson et al. working with *M. montanus* and *P. sungorus* suggested that the information transfer from mothers to their young ones occurs pre-natally and not during the lactation [7,8]. Klein and Reppert, et al. have reported that the melatonin passes from mother to the fetus as melatonin crosses almost every biological barriers including the placenta [9,10]. Zemdegs et al. working with sheep and ewe have suggested that due to apparent free transport of melatonin between the maternal and fetal compartment, fetuses were probably exposed to similar melatonin variations as their mothers. Depending upon the photoperiod to which the mother was exposed during gestation, the young ones respond it as either stimulatory or inhibitory [11]. However, our recent studies explained in detail the effect of maternal photoperiod on growth and sexual development of a seasonally breeding rodent *F. pennanti*.

Recently we have observed a retarded neonatal growth, when mother was kept under short day length (SDL: 10L: 14D) condition. On contrary to this, pups of constant dark (DD; 0L:24) condition experiencing mother exhibited significant increase in their growth. The DD pups attained a level of growth at the age of 40 days, which was equivalent to that of 60 days old pups delivered by natural day length (NDL; 12L: 12D) condition experiencing mothers [12]. The pineal gland weight and plasma level of melatonin in both male and female pups were retarded under constant light (LL; 24L: 0D) & long day length (LDL; 14L: 10D) conditions and enhanced under SDL & DD conditions only. As per report, SDL activates the pineal gland, hence melatonin synthesis and release [12].

However, in the pups reared under DD condition, the pineal gland weight and plasma level of melatonin was significantly decreased. According to the literatures, the increase in dark phase of light-dark cycle increases the level of melatonin [1]. However, no definite report for melatonin level is available under constant darkness in other mammals.

Surprisingly, we found that pups experiencing DD condition prenatally and postnatally exhibited low level of melatonin. This low level of melatonin in DD pups may be due to the following reasons:

1. The continuous melatonin secretion by the maternal as well as fetal pineal led to exhaustion of melatonin secreting cells, hence finally decreased the synthesis and release of melatonin in DD pups.
2. The continuous secretion of melatonin in DD experiencing mother, who conveyed it to the fetus through the placenta retarded the fetal pineal activity by the 'negative feed back mechanism' hence, fetal plasma level of melatonin decreased significantly. This favoured the idea of Horton [13], Stetson *et al* [14] who suggested that the information transfer from mothers to their young one occurs pre-natally and not during the lactation.

The major control of melatonin synthesis is exerted by post-ganglionic sympathetic fibres innervating the pineal gland. Nor-adrenalin normally released at night stimulates α- and β-subtypes of adrenergic receptors. Nor-adrenalin binds to membrane bound pinealocyte receptors activating adenyl cyclase activity through GTP-binding protein in the cell membrane and increases cAMP levels, which is required to activate NAT activity. Stimulation of NAT activity involves both transcription and translation. α/β-adrenergic stimulation inturn activate protein kinase C by translocation from the cytosol to the membrane. At this point protein kinase C also provides a feedback mechanism in that it desensitizes the α- adrenoceptor causing low level of NAT activity resulting in low level of plasma melatonin.

Recently, Stehle et al. have discovered a product of CREM (cyclic AMP-responsible element modulator) gene, highly expressed in pineal (and other neuroendocrine tissues), which encodes a potent repressor of cAMP-induced gene transcription. This inducible cAMP early repressor (ICER) shows a marked circadian rhythm in pineal [15].

ICER mRNA is induced at night under adrenergic control via cAMP. The peak of the ICER expression corresponds to the declining phase of NAT activity. Thus it is possible that the major component of negative feed-back loop regulating rhythmic gene expre-

ssion in the pineal is the marked decrease in NAT activity, which leads to low level of plasma melatonin.

Looking into the above results, it appears that whenever, there was an extension of dark period of light-dark cycle (more than the SDL photoperiod), the positive effect of pineal gland and its hormone-melatonin towards growth and sexual development of pups was noted. On the other hand, SDL condition influenced the growth and sexual development of pups negatively. Hence, the pups delivered by DD experiencing mother and reared under the similar condition exhibited better growth and sexual development. We know from the report of Gupta *et al* [16] that the growth hormone (GH) is inversely related to melatonin level in human prepubertal male and female. Therefore, a low melatonin level might have enhanced the GH level and due to this reason we observed the highest growth and sexual development in case of DD pups. Our such observations is in parallel with suggestion of Stetson [14] that exposure of gravid females to different photoperiodic conditions may have differential effect on young ones born and reared under same condition. Such a phenomenon of maternal photoperiodic transmission to her young ones definitely has an adaptive significance.

Therefore, the physiological level of maternal melatonin (pregnant or lactating) is of great importance for growth and sexual maturation in young rodents. Due to apparent free transport of melatonin between maternal and fetal compartments, fetuses are exposed to similar melatonin variation as their mothers. Fetal SCN expresses more melatonin binding sites and act as a target for maternal melatonin for the pre and post-natal expression and entrainment of circadian rhythms to decide the nocturnal and diurnal habits of the vertebrates [17].

Placental Transfer of melatonin:

Studies till date suggested the placental Transfer of melatonin in several mammalian species [11,14,18]. First, it was shown that a small amount of (^{3}H)- melatonin injected intravenously into pregnant animals during the later stages of gestation promptly appears in the fetal circulation and the rates of disappearance of radio-labelled melatonin in the maternal melatonin and fetal circulation are parallel. In another experiment, a diurnal change in maternal melatonin, experimentally stimulated on a reduced time scale, results in a rapid reflection of the rhythm in the fetal circulation. Rapid placental transfer of melatonin is quite predictable in view of the lipophilic, non-ionized properties of this small molecule.

Another important finding of the placental transfer study was observation of maternally derived (^{3}H) melatonin in the neonates. Since it has been shown that in the adult mammals, the melatonin rhythm in circulating levels is precisely reflected in cerebrospinal fluid, suggesting the expression of maternally generated melatonin rhythm in fetal cerebrospinal fluid as well as in circulation. Both routes may deliver the hormone on a daily basis to fetal brain structure where melatonin is secreted at night.

Maternal Pineal Gland and Post-natal Development:

In case of human, studies suggested that melatonin level in the umbilical artery and the umbilical veins of newly born females were not different from serum melatonin of their mother [18,19].

Recently, Bishupuri and Haldar [20] suggested that females treated with daily evening melatonin injection (dose: 20mg/0.1ml of normal saline/100g body weight/day at 5.00 to 6.00 pm) during lactation period negatively influenced the neonatal growth and sexual maturation by maternal hormonal transfer of melatonin either prenatally through the placenta or via the mother's milk.

We have also observed that melatonin treatment either to mothers or to pups exhibited inhibitory effect on their growth and sexual maturation. Melatonin administration was always observed to be pro-estrogenic and anti-progesterogenic both to mothers and pups. The female pups of melatonin treated mothers have reduced ovarian/uterine weight, decreased progesterone and increased estradiol, hence a delay in attaining the sexual maturity. In male pups testosterone level was low, hence a delayed spermiogenesis was noted. Hence, it appears that melatonin directly suppresses the level of GH and delayed puberty by suppression of gonadal steroid and thyroid gland function (expressed by low circulating T_4). Further low level of thyroxine also reduces growth and skeletal muscle development.

Our results favoured the idea of Davis that melatonin is the fetus's window to periodicity of outside world. Through melatonin, the fetus "knows" what time of year it is [17]. The major function of melatonin during development is to communicate information about photoperiod and thereby regulate growth and sexual development. Here, it is also to be noted that extension of dark phase of light-dark cycle is more effective in term of their stimulatory/ inhibitory effect on the growth and sexual development of offspring than the light phase. Therefore, we may suggest that the exposure of different groups of gestational females to different photoperiodic conditions have different effects on the growth and sexual development of young ones.

In conclusion, the phototherapy appears to be one of the safest clinical therapies for pregnant females to promote the fetal growth and there comes the role of melatonin – the wonder molecule.

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