

Opposite influence of light and blindness on pituitary–gonadal function

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Some environmental factors may influence the pituitary–gonadal function. Among these, light plays an important role in animals and in humans. The effect of light on the endocrine system is mediated by the pineal gland, through the modulation of melatonin secretion. In fact, melatonin secretion is stimulated by darkness and suppressed by light, thus its circadian rhythm peaks at night. Light plays a favorable action on the hypothalamic–pituitary axis likely inhibiting melatonin secretion, while the exogenous melatonin administration does not seem to impair the hormonal secretions of this axis. The basal and rhythmic pituitary–gonadal hormone secretions are regulated by a central clock gene and some independent clock genes in the peripheral tissues. Light is able to induce the expression of some of these genes, thus playing an important role in regulating the hormonal secretions of pituitary–gonadal axis and the sexual and reproductive function in animals and humans. The lack of light stimulus in blind subjects induces increase in plasma melatonin concentrations with a free-running rhythm of secretion, which impairs the hormonal secretions of pituitary–gonadal axis, causing disorders of reproductive processes in both sexes.

Keywords: light, blindness, clock genes, melatonin, pituitary–gonadal function

INTRODUCTION

Several endogenous and exogenous factors may influence endocrine secretions (1), including those of pituitary–gonadal axis (2). Among the exogenous environmental factors, light seems to play a pivotal role both in animals and in humans, especially as synchronizing agent of hormonal rhythmicity (3–5). Several structures are involved in the mechanism of transmission of light stimulus to the circadian timing system: a retinal component with photoreceptor and ganglion cells, a retino–hypothalamic tract (RHT) originating from these and projected to the suprachiasmatic nucleus (SCN), the circadian pacemaker, i.e., the SCN, efferent projections of SCN to a series of hypothalamic and thalamic nuclei (6). The major projections are to areas that themselves receive retinal input and project reciprocally to the SCN. Of particular importance are the projections of the SCN that reach the supraventricular zone and then the hypothalamus because they provide, among other functions, the neuroendocrine regulation and the pineal melatonin secretion, which plays an intermediate role between the environment and the endocrine system. Studies on the effects of light on the endocrine secretions in animals are usually performed by exposing them to different photoperiods or rendering them blind. In humans, blindness may be considered, despite unlucky, an experimental condition to study the effects of light on the hormonal secretions, but in this regard data are scarce and sometimes controversial. However, since light is one of the most important environmental factors, paying attention to its influence on the endocrine system may avoid misleading interpretation of individual hormonal data and may help prevent alterations in hormonal pattern and rhythmicity caused by variations of this environmental entraining-agent.

MOLECULAR ASPECTS

The recent identification of several clock genes in a number of organism, including mammals (7–14), seems to assign a pivotal role to the hypothalamus as pacemaker of pituitary–gonadal secretions. However, the findings of independent clocks in peripheral tissues (1, 9, 12–15) suggest a possible gonadal independent role in regulating the rhythmicity of gonadal steroids. In fact, recent findings support the assumption that some clock genes can influence fertility and testosterone (T) seasonality both in animals (16) and in humans (17). In particular, *Brain and muscle Arnt-like protein 1 (BMAL1)* and *Neuronal PAS domain protein 2 (NPAS2)* gene variants have been shown to influence fertility and seasonality in humans (17). Anyway, since light plays an important synchronizing role on the circadian rhythmicity, the alteration of photoperiod, or the lack of light stimulus, as occurring in blindness, may impair this rhythmicity (18). Consequently, the desynchronizing effect of altered light signal may influence circadian peripheral clocks in female and male reproductive tissues causing impairment of fertility (19) with disorders in estrus cycles, ovulation, sperm generation, implantation, and the progression of pregnancy (14).

In fact, light may act at molecular level inducing the expression of some immediate early genes in the SCN involved in entrainment of circadian clock (20, 21). These genes, activated by light, encode transcription factor proteins involved in molecular mechanism of resetting the circadian clock (20). Among these genes, are *c-fos* and *nur 77*, two of the early-response genes known to be induced in the SCN by light, and *egr-3*, a zinc-finger transcription factor, whose induction by light seems to be restricted to the ventral SCN, a structure involved in entrainment (22). Light also induces *Jun-B* messenger RNA expression and *AP-1* activity in the SCN (20).

Moreover, other mammalian genes involved in circadian regulation, like *mper 1* and *mper 2* have been shown to be expressed in SCN under light stimulus control (23). It has been demonstrated that light stimulus induces expression of *C-fos* gene in postnatal rat retinas (24). The earliest expression occurs between postnatal days 11 and 15 and is correlated to the genes coding for proteins involved in phototransduction, suggesting that it may play a role in the regulation of these genes in retinal cells during the light/dark cycle (24). This could in part explain the severe alteration of hormonal rhythmicity in born blinds. Further evidence that genes involved in clock regulation are reset by light has been given by studies in *Neurospora* (25). In particular, the *white collar-1* (*wc-1*) and *white collar-2* (*wc-2*), both global regulators of photoreponses in *Neurospora*, encode DNA binding proteins containing PAS domains and acting as transcriptional activators, thus playing an essential role in the organization of circadian rhythmicity. Similarities between the PAS domain regions of molecules involved in light perception and circadian rhythmicity in several species suggest an evolutionary link between ancient photoreceptor protein and more recently described proteins required for circadian oscillation (25, 26).

ROLE OF PINEAL GLAND AND MELATONIN

The effects of environmental light on the hypothalamic–pituitary–gonadal axis are mediated by the pineal gland, through melatonin secretion (27, 28). Light stimulus from the environment reaches the retina; from here, through a RHT reaches the SCN, then the superior cervical ganglion, and finally the pineal gland, where it exerts an inhibiting effect on the pineal melatonin secretion. Instead, the darkness activates alpha1 and alpha2-adrenergic receptors in pineal gland, then it increases cyclic AMP and calcium concentration and activates arylalkylamine *N*-acetyltransferase, thus initiating the synthesis and release of melatonin, whose circadian rhythmicity is under control of an endogenous free-running pacemaker located in the SCN (29). As result of the opposite effect of light and darkness, melatonin rhythm normally peaks at night both in animals and in humans (29). Light exposure at night induces a parallel reduction in both plasma and salivary melatonin (30). A little amount of melatonin may be synthesized directly by retina: melatonin synthesis in cultured neural retinas of golden hamster exhibits a circadian rhythm entrained by light/dark cycles applied *in vitro*, whereas it shows a free-running rhythm when the culture is held on constant darkness (31). Several melatonin receptors have been found and cloned in animal and in humans. They belong to a superfamily of G-protein coupled receptors and mediate the physiological actions of melatonin with different specificity (29, 32–36). Among these, of particular importance are Mel 1a, isolated in brain, SCN, and pituitary, which is involved in circadian and reproductive processes (29, 32, 34); Mel 1b, isolated in retinas and brain, which is involved in retinas physiology regulation in some mammals (33); and Mel H9, isolated in pituitary, which is likely involved in genetically based neuroendocrine disorders (35).

Blindness affects melatonin secretion significantly. Blind patients show increased day-time melatonin levels or more complex changes in circadian rhythmicity (36–39). They exhibit a phase-advanced or a phase-delayed rhythm with respect to that of normal subjects. However, the exposure to bright light may

suppress the high melatonin levels in some blind subjects with functional integrity of the RHT (40, 41). In fact, their melatonin secretion may be suppressed when their eyes are exposed to a bright light stimulus. Interestingly, these patients were less suffering for sleep alterations. The authors who studied these patients concluded that some blind people can have a functional integrity of RHT, allowing a melatonin suppression when exposed to light stimulus and consequently a sufficient sleep entrainment. Instead, blind patients with complete absence of bright input to the circadian system may represent a distinct form of blindness, associated with periodic insomnia correlated to abnormalities of melatonin rhythm, due to the persistent lack of synchronizing effect of light (40). In fact, changes in melatonin rhythmicity are more severe in patients with total blindness compared to those with only light perception (42). Interestingly, a reduced incidence of cancer has been observed in blind people (43). Even if other explanations have to be considered, the protective effect of high melatonin concentrations may not be excluded (43).

LIGHT, BLINDNESS, AND HYPOTHALAMIC–PITUITARY–GONADAL FUNCTION

Light influences favorably gonadal function in animals and this effect seems to be mediated by reduction of pineal melatonin production, whereas a reduction of photoperiod impairs this function through an activation of melatonin secretion (27, 28, 44). Sexual activity in animals is reduced during the months of the year with short day; this reduction is prevented by pinealectomy (28, 44). Moreover, increased melatonin levels and reduction of plasma luteinizing hormone (LH), follicle-stimulating hormone (FSH), prolactin (PRL), T levels, testis weight, spermatozoa production, and sexual activity have been documented in animals rendered blind or exposed to a short photoperiod (44–48). These effects are prevented by pinealectomy (28, 45). Seasonal variations in luminosity influence melatonin secretion and some functions correlated not only in animals (28) but also in humans. Women living in Finland, a region with a strong seasonal contrast in luminosity, showed increased melatonin and reduced gonadotropin secretion during dark season, with consequent reduction of conception rates (49). Seasonal variations of plasma LH and T concentrations have been demonstrated also in patients with primary and secondary hypogonadism, but with peak of values in season different from that of normal subjects (18). A possible negative feed-back mechanism between melatonin and hormones of pituitary–gonadal axis seems to be suggested by the presence of gonadotropin and gonadal steroid receptors in human pinealocytes (50) and conversely of melatonin receptors in human hypothalamus, pituitary, and in other tissues of gonadal tract (51). Other findings, instead, suggest that there is no classic feed-back between the pineal gland and the testes (52) and that administration of exogenous melatonin does not impair pituitary–gonadal hormone secretion in men (53); on the contrary it seems to amplify pulsatile LH secretion in women (54). However, this is in contrast with that occurring in patients with chronic endogenous melatonin increase that may show alterations of menstrual cycle in case of women (28, 55) and oligospermia or azospermia in case of men (56).

Blindness can influence gonadal function in humans. Data on the age of puberty onset and fertility in blind women are

conflicting. Menarche in blind girls has been described as being advanced or delayed (57–59) and fertility in adult women as being normal or impaired (60, 61). Some blind adult patients showed a normal secretory rhythm of LH, FSH, and T in spite of impaired cortisol rhythm (62). However, in this study, the majority of patients had become blind from 14 years onward, an age in which mechanisms involved in pubertal development and gonadal function are quite completed. Instead, in a group of institutionalized blind boys, whose blindness was started in the first years of life, we found impaired basal and stimulated plasma levels of LH, FSH, PRL, and T (63). Since similar alterations had been described both in hypogonadotropic hypogonadism and in delayed puberty (64, 65), several years ago we studied the same hormonal pattern in a group of institutionalized adult blind males aged 20–29. They were divided in two subgroups: 14 with total blindness and 21 with only light perception, whose age of onset of impaired vision was reported by them as the first 5 years of life (36). Both subgroups showed increased plasma melatonin levels in comparison with a normal control group of sighted subjects, but normal LH, FSH, PRL, and T levels. However, the finding of a significant increase of FSH/LH ratio in both subgroups of blind patients versus the control group, could indicate a possible subclinical impairment of testicular function that however should be verified with studies of dynamic hormonal secretions and of seminal patterns, which the patients did not consent.

In conclusion, taking into account the data appeared in the literature and the results of our previous studies, light stimulus seems to influence favorably gonadal function both in animals and in humans, likely through inhibition of melatonin secretion. Instead, the lack or reduction of light stimulus in humans can induce:

- increased plasma melatonin concentrations;
- impairment of gonadotropins, PRL, and T secretion in pre-pubertal blind boys causing delayed puberty or more severe hypogonadism;
- impairment of pubertal development in young blind girls and of ovarian function and fertility in blind adult women.

These alterations seem to be more severe when the blindness occurs in the first years of life.

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