ASSOCIATION OF MELATONIN SECRETION WITH SEASONAL LUMINOSITY IN HUMAN SUBJECTS

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Background
During 1980-1983 I was a scientist and General Secretary in the Nordic Council of Arctic Medical Research (NCAMR). This organization belonged to the Nordic Council of Ministers, and its office was situated at the University of Oulu, Finland. One of the purposes of NCARM was to promote scientific research related to adaptation of circumpolar people to their environment. My research interest was partly directed to mechanisms by which environmental stimuli are translated to hormonal responses and, therefore focused on brain, hypothalamic and pituitary hormones. At NCAMR I decided to initiate studies on the effects of luminosity on bodily functions. An important subject for such studies is the pineal hormone melatonin that is rigidly controlled by the amount of light reaching the eyes.

Development of melatonin radioimmunossay
Our laboratory already had a long experience of radioimmunoassays and we started to immunize rabbits against a melatonin conjugate to set up a method to measure the concentrations of this hormone in biological fluids. At the time the tracer used in melatonin radioimmunoassays was tritiated melatonin. Since the tritium marker in the melatonin molecule was very weak, as it in any molecule, and since we did not have a beta-counter for tritium measurements in our laboratory, we decided to use highly radioactive iodine as a marker. We knew then that the tyrosine and histidine moieties were the only ones that were able to react with iodine. Therefore we tried to couple histidine to melatonin for radioiodination. For some reason the coupling of histidine to melatonin did not succeed, but we observed an iodinated compound in the reaction mixture that also bound to the melatonin antiserum. Later, using mass-spectrometry and NMR analyses we were able to show that iodine was indeed bound to the position 2 of the melatonin molecule itself (1). It was a novel finding that melatonin, in addition to histidine and tyrosine moieties, was able to incorporate iodine, though the rate of the incorporation was much slower. Using this tracer we were able to set up a very sensitive radioimmunoassay for the measure-
ments of melatonin in biological fluids (2). Since this work was partly supported by the NCARM, we made the new melatonin tracer available to scientists interested in projects related to arctic medicine. This offer is still open. The incorporation of iodine into the nucleus of the melatonin molecule was fortunate in another very important way. The new compound retained full biological activity and could be used for studies of the localization and characterization of melatonin receptors. That happened in other laboratories later.

**Seasonal secretion of melatonin**

It has been known for a long time that melatonin is secreted during the night in all species so far studied. Light suppresses the enzymes inducing melatonin synthesis and in the absence of light melatonin synthesis is stimulated. Melatonin thus appears to be a messenger that announces to organisms that night has begun (3). In some species melatonin secretion was also found to follow a seasonal rhythm. As the amount of light increases during spring and summer, melatonin secretion decreases (4). Some circumpolar species that are exposed to continuous polar day e.g. seals and reindeer stop their melatonin secretion almost totally in spring and summer (5).

Several laboratories, including our own, have studied melatonin secretion in circumpolar areas and demonstrated that human subjects living at latitudes 60-70°N exhibit higher circulating melatonin levels in winter than in summer (6-11). Interestingly, subjects overwintering in Antarctic bases did not exhibit seasonal changes in plasma melatonin nor in urinary melatonin metabolite levels, in spite of the season-long polar night. However, their daily maximum of the melatonin rhythm became phase-delayed by 4 hrs in winter (12-13). The seasonal phase delay of the melatonin rhythm exists also in subjects from lower latitudes, but is being only 1-2 hrs, is clearly shorter (14). This phase delay may be linked to depressive symptoms occurring in some persons in winter.

In a recent study we collected night-time urinary samples from 20 healthy male subjects living in northern counties of Finland (67-68°N) every two months and followed their seasonal melatonin secretion. We observed that melatonin secretion was twice as high in December as in April (0.88 nmol/12h vs. 0.43 nmol/12h), indicating the presence of a distinct seasonal rhythm in human subjects as well (11). Why this rhythm was not evident in Antarctica (12), was perhaps due to the fact
that during the Antarctic winter the subjects could spend outdoors only less than one hour in a day. Our subjects from northern Finland were exposed to an outdoor climate for 6-8 hrs daily throughout the year and exhibited a distinct seasonal rhythm (11).

We were also able to study the association between melatonin secretion and radiation from the sun (11). The meteorologic data was obtained from the nearby Sodankylä observatory. The solar radiance was divided into global irradiance (radiance measurements directed vertically upwards) and reflected irradiance or albedo (radiance measurements directed vertically downwards). We observed that in April, when the polar night had ended and there was still a snow cover, the albedo was greater than the global irradiance. Regression analyses confirmed this situation and showed that there was a significant negative correlation between albedo and melatonin secretion (R= -0.34). The correlation was clearly less evident with global irradiance. Interestingly, temperature bore no association with melatonin secretion.

It therefore appears that when the viewing angle of the eyes in humans is mostly directed downwards, the radiation reaching the eyes via the snow is most effective in suppressing melatonin secretion. This albedo effect is also of biological significance in animal species and the snow cover in spring may be an early cue for starting migration and reproductive activity.

**Melatonin and reproductive competence**

The seasonal secretion of melatonin is related to reproductive cycles so that in long-day breeders melatonin appears to inhibit reproductive hormones while it stimulates them in short-day breeders (4). Seasonal reproductive activity is not prominent in humans, but recent statistics (e.g. in Finland) show that deliveries are 12% higher in March than in other months. This suggests that conception is more frequent in May-June, when the environmental luminosity is highest. It therefore appears that melatonin is associated with reproductive competence. However, the data to support this, at least in human subjects, is mostly indirect. Studies in northern Finland show that low circulating melatonin levels in spring and early summer coincide with elevated pituitary gonadotrophin and ovarian steroid levels, as well as with stimulated folliculogenesis (8,9,15). Furthermore, melatonin levels in preovulatory follicular fluid are lower in summer than in winter (16). These observations, together with the increased conception rates in spring
and early summer, suggest an anti-gonadotropin role for melatonin in human subjects. This role implies that increased luminosity in spring reduces circulating melatonin concentrations, leading to increased secretion of hypothalamic gonadotropin-releasing hormone, pituitary gonadotropins, ovarian steroids and, eventually to the stimulation of reproductive activity. In a recent *in vitro* study physiological doses of melatonin administered to cultured human granulosa cells were found to increase the messenger RNA levels of the gonadotropin hormone receptor in the ovarian cells and stimulate gonadotropin-induced progesterone levels (17). These direct findings diverge somewhat from those dealing with reproductive hormones, since it is the high serum melatonin levels that associate with low serum gonadotropin and ovarian steroid levels.

**Melatonin and self-destructive behavior**

Most of us have experienced that the increasing luminosity in spring disturbs our sleep-wake rhythm. Another biological effect human subjects encounter in spring is an increase in self-destructive behavior. Suicides in several northern countries show an increased occurrence in spring (18-23). For example a study from Belgium shows a maximum of violent suicide cases occurring around 15\textsuperscript{th} of May (23). The roles of meteorological and other factors as precipitous agents of suicidal activity have been widely studied. Elevated ambient temperature, low tryptophan availability, increased sunshine duration and low day-time plasma melatonin levels often precede the fatal outcomes (22-26). As far as melatonin and solar radiation are concerned, previous studies have not been reliable in this respect. Day-time melatonin represents only a minor fraction of the hormone secreted during a 24 h day. It should be noted that low night-time plasma melatonin levels have recently been observed to be related to sleep disturbances that can be successfully treated with low doses of oral melatonin (27). Also estimations of solar radiance from calendars and/or from sunshine records may not be reliable indicators of the true amount of light reaching the eyes. It is possible that melatonin administration and the use of thight curtains in spring provide us with some protection from the deleterious effects of sunshine on our sleep patterns and even to self-destructive thoughts.
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