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Chronobiology, Melatonin, and Sleep in Infants and Children

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Sleep disturbances in children, such as frequent night waking or difficulty in settling, are a common problem reported to health care providers. These problems are disruptive and can cause stress for parents or caregivers. A number of factors associated with sleep disturbances in children are described in the literature, including developmental, environmental, and/or psychosocial factors. Chronobiology and the part that melatonin plays in sleep are lesser-known factors associated with sleep disturbances that have recently become of interest. The development of the sleep-wake cycle in children and the role of melatonin in this cycle are described. Factors that are associated with alterations in melatonin production, such as light, medications, and food are discussed. Strategies for maintaining a synchronized melatonin rhythm that may be a beneficial adjunct in the treatment of sleep disturbances in children are presented.

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Sleep disturbances in children, such as frequent night waking or difficulty in settling at bedtime, are common problems reported to health care providers. Sleep disturbances have been reported in 13-40% of children under the age of 4 (Adair, Bauchner, Philipp, Levenson, & Zuckerman, 1991; Johnson, 1991; Kateria, Swanson, & Trevarthin, 1987; Richman, 1981). A child who wakes frequently throughout the night or resists going to bed is disruptive to the entire household and can cause a significant amount of stress for parents or caregivers. New parents may question their competence as caregivers, and more seasoned parents may find the differences in the sleep habits of a subsequent child disconcerting. Frequent night wakings for parents can result in a decrease in performance and increased accidents at work, at home, or while commuting (Marcus & Loughlin, 1996; Torsvall, Akerstedt, Gillander, & Knutsson, 1989). For children, sleep disruption can adversely affect the developmental processes of the brain (Smith, 1995).

A number of factors associated with sleep disturbances in children are described in the literature, including developmental, environmental, and/or psychosocial factors. Factors reported include prematurity (Walker, 1989), adverse perinatal events such as long labor (Richman, 1981), gender (Van Tassel, 1985), birth order (Edgil, Wood, & Smith, 1985), method of feeding (Elias, Nicolson, Bora, & Johnston, 1986), temperament (Atkinson, Vetere, & Grayson, 1995; Jimmerson, 1991; Scher, Epstein, Sadeh, Tirosh, & Lavie, 1992; Van Tassel, 1985), parental presence at bedtime (Adair et al., 1991), environmental stress (Kateria et al., 1987; Richman, 1981), and maternal mental health (Richman, 1981; Van Tassel, 1985). A number of co-morbid conditions associated with sleep disturbances are noted in the literature, such as asthma (Sadeh, Horowitz, Wolach-Benodis, & Wolach, 1998), attention deficit–hyperactivity activity (Ring et al., 1998), severe learning disability (Bramble, 1997), autism (Richdale & Prior, 1995), abuse (Glod, 1994), and elevated lead levels (Owens-Stively, Spirito, Arrigan, & Alario, 1997). Despite the wide accumulation of information, the exact causes of sleep disturbances in children are still unknown and most likely result from a combination of a variety of contributory factors. Overall, sleep disturbances are a subjectively personal topic for parents that require education and patience. A lesser-known factor associated with sleep disturbances is that of chronobiology and the part circadian rhythms play in sleep.

Chronobiology

Chronobiology is the study of biological rhythms (see Table 1). All living organisms exhibit cyclicity and biological rhythms that serve as basic organizing features for the individual (Florez & Takahashi, 1995). Cycles are apparent in all aspects of life that include the solar system, plant growth, and light/dark environment. These processes in humans cut across a wide range of frequencies, from seconds (e.g. the heartbeat) to that of weeks (e.g. the menstrual cycle) (Florez & Takahashi, 1995). Rhythms with periods of 24 hours ± 4 hours are termed circadian rhythms. The secretion of the pineal hormone melatonin, the sleep-wake cycle, and the physiological variable of body temperature are examples of circadian rhythms in humans and are closely linked to efficient sleep. Humans also exhibit rhythms shorter than 24 hours, termed ultradian rhythms, and longer than 24 hours, termed infradian rhythms (Refinetti & Menaker, 1992). Infants initially exhibit ultradian rhythms in their sleep-wake and food intake cycles, waking frequently and feeding often. These rhythms then progress to a more mature circadian

Table 1. Chronobiology Terms

Chronobiology – the study of biological rhythms
Rhythm – the regular occurrence of a sequence of events in the same order at the same interval
Circadian rhythm – rhythm with a period of 24+/-4 hours
Ultradian rhythm – a rhythm with a period less than 24 hours
Infradian rhythm – a rhythm with a period of greater than 24 hours
Period – the time to complete one cycle of the rhythm
Phase – the position of the rhythm in relation to time
Phase shift – displacement of the rhythm along the time axis
Synchronization – entrainment of the rhythm to a set interval
Desynchronization – dysrhythmia of circadian rhythms
Oscillators – an endogenous circadian pacemaker
Zeitgebers – environmental or social factor that influences biological oscillators

pattern as they age (Lohr & Siegmund, 1999). Endogenous biological clocks termed oscillators are pacemakers that are influenced and entrained by the period changes of a set of environmental factors (also referred to as "synchronizers" or "zeitgebers") such as light and temperature (Ashkenazi, Reinberg, Bicakova-Rocher, & Ticher, 1993). Extremes of these same environmental factors can shift the phase of oscillators, causing disruptions in physiological processes. It has been suggested that both environmental (photic) cues and non-photic (social) cues act to entrain human circadian rhythms (Elmore, Betrus, & Burr, 1994; Honma et al., 1995; McGraw, Hoffmann, Harker, & Herman, 1999).

Sleep-Wake Circadian Rhythms

There initially exist several ultradian periods (i.e., 4, 6, 8, and 12-hour periods) that appear throughout an infant's development to influence sleep-wake and food-intake behaviors, which extinguish in favor of periods of 12 and 24 hours at around the twelfth week of life (Lohr & Siegmund, 1999). Starting around the eighteenth week of life (4 to 5 months), infants have a well-established circadian sleep-wake rhythm with sleep spans greater than or equal to 400 min (6 hours) occurring between 22:00 and 05:00. (de Roquefeuil, Djakovic, & Montagner, 1993; Kleitman & Engelmann, 1953). Certain ages herald changes in the frequency and length of sleep spans – a child 5 to 10 months old has on average four sleep spans in a 24-hour period; a child 11 to 15 months has an average of three sleep spans, and; a 13- to 15-month old has two sleep spans in a day (de Roquefeuil et al., 1993).

Melatonin

The suprachiasmatic nucleus (SCN), which is located in the hypothalamus, is the main endogenous pacemaker responsible for the timing of physiologic processes (Recio, Miguez, Buxton, & Challet, 1997), to include the sleep-wake cycle, temperature, hypothalamic-pituitary-gonadal axis, and melatonin (Voultsios, Kennaway, & Dawson, 1997). Melatonin is important in the maintenance of biological rhythms and has been widely accepted as a useful marker of the circadian clock in humans because its secretion is essentially directly controlled by the SCN (Voultsios et al., 1997). Melatonin is a product of tryptophan metabolism and is secreted into the general circulation by the pineal gland (an end organ of the visual system) mainly during the hours of darkness when, in the absence of bright light, the SCN is electrically active (Reiter, 1991a). In response to light, ganglion cell axons from the retinas of the eyes synchronize the activity of the SCN to precisely 24 hours (Davis, 1981). Melatonin rhythms free (do not conform to a 24-hour circadian period) with a period of more than 24 hours under conditions of total darkness, such as in the blind (Lewy & Newsome, 1983). No melatonin rhythm is observed under continuous lighting conditions (Reiter, 1991a). A circadian pattern of melatonin is found in serum, saliva, cerebrospinal fluid, amniotic fluid and numerous tissues (Reiter, 1991a). Highest melatonin levels are always associated with the dark. Melatonin has been referred to as the chemical expression of darkness (Reiter, 1991b).

There is considerable evidence linking melatonin to the sleep-wake cycle. In healthy individuals with mature circadian rhythms, melatonin begins to rise as the sun sets, reaches a peak at around 02:00, and then gradually falls to almost undetectable levels during the day (Cavallo, 1993). Body temperature follows an inverse cycle to that of melatonin with variations of about 0.4° C that peak in the late afternoon and trough between 03:00 and 06:00 (Cagnacci, Krauchi, Wirz-Justice, & Volpe, 1997). Temperature is higher during the day while a person is awake secondary to physical activity, which generates heat, and lower at night when metabolism is at a minimum. The fall in temperature and subsequent rise in melatonin in the evening hours is what induces drowsiness and ultimately sleep. This inverse relationship between core body temperature and melatonin has been known for years (Saarela & Reiter, 1994), however the direct relationship or association between the two is still unclear (Cagnacci et al., 1997). Disrupted patterns of melatonin secretion and decreased melatonin production have been associated with sleep problems in blind children and the elderly (Espezel, Jan, O'Donnell, & Milner, 1996; Haimov et al., 1994), and alterations in the rhythm of body temperature have been associated with insomnia in a number of studies (Lack, Balfour, & Kalucy, 1985; Morris, Lack, & Dawson, 1990). Altered secretion of melatonin, either levels too high or too low, has been observed with a number of other conditions, such as amenorrhea, anorexia nervosa, and a variety of mood disorders (Reiter, 1991a). Melatonin also is a ubiquitously acting free radical scavenger and effective antioxidant (Reiter, 1998), a potent inhibitor of certain types of tumors, and is known to stimulate immune response (Reiter, 1991a).

Melatonin ingested orally seems to have a mild, sleep-inducing effect and can regulate sleep-wake disorders (Shochat, Luboshitzky, & Lavie, 1997), however the timing of administration is very important, being most effective when it is administered at the time of the onset of endogenous melatonin secretion (Tzischinsky & Lavie, 1994). Melatonin that is administered

20-30 minutes before bedtime at approximately the same time each night induces sleepiness within half an hour (Jan, Freeman, & Fast, 1999). The administration of exogenous melatonin has been successful in the treatment of circadian rhythm sleep-wake disorders seen in the blind, mentally retarded, and other disorders that have diminished ability to perceive and interpret synchronizing cues (Jan & O'Donnell, 1996; Palm, Blennow, & Wetterberg, 1997). There is little evidence to support the use of melatonin in otherwise healthy children, and therefore, indiscriminate use is not recommended. The inappropriate administration of melatonin can interfere with sleep processes by causing an irregular sleep-wake cycle (Middleton, Stone, & Arendt, 1996).

A number of studies have described the development of the circadian secretion of melatonin in childhood (Attanasio, Borrelli, & Gupta, 1985; Kennaway, Stamp, & Goble, 1992; McGraw et al., 1999; Sadeh, 1997). The day-night melatonin rhythm normally develops in newborns between the fourth and sixth month after birth, more-or-less coinciding with the development of a normal sleep-wake cycle (Waldhauser et al., 1988). Infants with immature patterns of melatonin secretion have poorer nocturnal sleep (Sadeh, 1997). Melatonin levels increase to peak between 1 and 3 years of age (Sadeh, 1997). Serum concentration then begins to decline, with nocturnal concentrations of melatonin being significantly higher in children 1 to 5 years of age than those 6 to 10 years of age and continues to decline in the subsequent age ranges (Attanasio et al., 1985; Reiter, 1992).

Maternal melatonin crosses the placental barrier and fetal melatonin levels approach concentrations similar to those found in maternal venous blood (Recio et al., 1997). This interchange begins the entrainment of the fetus to the 24-hour rhythm of the extrauterine environment. However, after birth, without the influence of the mother's circulating melatonin, an infant's sleep-wake rhythm will free run (does not conform to a 24-hour circadian period) until entrainment by environmental and social cues at around 16 weeks (McGraw et al., 1999). This is the result of the lower levels of melatonin that lack a rhythm in infants less than 3 months of age. Melatonin present in breast milk may aid in the synchronization of breast fed infants as long as the mother's circadian rhythms are synchronized and she is not substituting breast milk that has been pumped during the day for nighttime feedings (Recio et al., 1997).

Alteration of Melatonin

Exposure to light during the night abruptly decreases melatonin production and results in a rapid decline of the hormone in the circulation that approach basilar daytime levels (Reiter, 1991a; Reiter, 1991b). Brief light exposure of less than 1 minute (Reiter, 1991a) at levels greater than 300-400 illumination (lux) (Bojkowski et al., 1987) is all that is needed to induce this suppression. Upon return to darkness, values do not reach pre-exposure levels for at least 40 minutes (Lewy, Wehr, Goodwin, Newsome, & Markey, 1980). An average 10-ft. X 12-ft. room with a light fixture containing four 60-watt light bulbs would produce approximately 300 lux. Just as higher levels of lux are able to suppress melatonin, different wavelengths of light are more effective at suppressing melatonin (Reiter, 1985). Light of a shorter wavelength, such as green and blue light, is most effective at inhibiting pineal melatonin production, whereas light of a long wavelength, such as red light has little effect (Morita & Tokura, 1998).

The administration of aspirin, ibuprofen, or other nonsteroidal anti-inflammatory drugs (NSAIDs) during nighttime hours has been shown to suppress melatonin synthesis (Murphy, Myers, & Badia, 1996). It is believed that the inhibitory effects of NSAIDs on prostaglandin synthesis causes attenuation of the body's normal nocturnal body temperature decrease, resulting in a suppression of melatonin secretion. Normally, a person's body temperature exhibits a decline of greater than 0.4° C in the early evening and a subsequent rise in melatonin. However, in individuals who ingested a single dose of an NSAID at night, this decline was flattened and the subsequent melatonin secretion was suppressed. This may explain why NSAID use results in alterations in normal sleep patterns for some individuals (Murphy et al., 1996).

A number of plants have been shown to contain melatonin with varying amounts present in each species (Reiter & Kim, 1999). Plants with some of the highest melatonin levels are those of the family Cramineae, which includes rice, sweet corn, and oats (Hattori et al., 1995). When these foods are ingested, melatonin is absorbed via the gastrointestinal tract into the circulation and may reach levels sufficient to influence physiological processes (Hattori et al., 1995). Foods containing tryptophan, a precursor of melatonin, such as poultry, may also increase melatonin synthesis and, therefore, its physiological effects.

Implications for Patient Care

Breast fed infants ingest small amounts of maternal melatonin (35-80% of the maternal serum concentration) from their mother's breast milk (Illnerova, Buresova, & Presl, 1993), giving breast fed infants an advantage over formula fed infants. This is a good reason to encourage mothers to breast feed, especially in the first 3 months of life when melatonin synchronization is taking place (Recio et al., 1997). Since exposure to bright light significantly decreases serum melatonin concentration, it is wise for breastfeeding mothers to stay in relative darkness at least 1-2 hours before the first nocturnal feeding and to breast feed during the nocturnal hours in the dark, under low-level light (less than 100 lux such as a single 4-watt bulb), or with a nightlight equipped with a red light bulb (Recio et al., 1997). They should also maintain a stable sleep-wake routine so that their own melatonin secretion is properly synchronized. Ingestion of foods high in melatonin in the evening prior to nocturnal feedings would be beneficial. Mother's of breast fed infants should also avoid the use of NSAIDs, particularly during the nighttime hours. When a mother begins to wean a child the last feeding to be eliminated should be the nighttime feeding between 24:00 and 04:00, so as not to deprive the child of the maternal melatonin (Recio et al., 1997).

An additional consideration for newborns that should be addressed with parents is that of the lighting conditions during the daytime hours. Often parents want to keep a napping newborn in a dark room during the day, when it may be beneficial to keep them in a well-lit room (preferably natural daylight) in order to aid in the synchronization of their circadian clock.

For older children, many of these synchronizing activities are also important. Just as with infants, older children should nap in a well-lit room during the day in order to maintain synchronized rhythms. Obviously, permitting a child to sleep in a well-lit room at night should always be avoided. If a child awakens at night, turning on a bright light is not recommended. If a night light is needed, a red light bulb or a bulb that emits less than 100

Table 2. Strategies for Minimizing Desynchronization

For Mothers

- Breast feed for at least the first 3 months.
- Maintain a consistent sleep-wake schedule.
- Breastfeed in the dark, under dim light (< 100 lux) or red light at night.
- Eat melatonin- and tryptophan-rich food in the evening.
- Avoid NSAIDs, particularly at night.
- When weaning, eliminate the 24:00 – 04:00 feeding last.

For Children

- Newborns and older children should sleep in a dark room at night and nap in a well-lit room during the day.
- Use a dim light (< 100 lux) as a nightlight or one with a red light bulb.
- Maintain a nighttime routine.
- Provide melatonin- and tryptophan-rich foods at dinner.
- Avoid the use of NSAIDs unless fever present, particularly at night.

lux has little effect on melatonin. Maintaining a nighttime routine is very important for children of all ages. Since it is suggested that melatonin synthesis is entrained by social as well as environmental factors, maintaining a routine of activities that occur just prior to bedtime and upon rising in the morning may help to synchronize a child's circadian rhythms (Recio et al., 1997). The use of NSAIDs at night should be avoided if at all possible. However, if a child has a fever the administration of an NSAID would be warranted since the results of an uncontrolled fever are much more detrimental than disrupted melatonin production. Elevated temperatures will have a disruptive effect on melatonin synthesis; prompt fever reduction will aid in sleep. Finally, the ingestion of melatonin- and tryptophan-rich foods at dinner may aid in establishing and maintaining synchronized melatonin rhythms (see Table 2).

Sleep disturbances in children are common and are a source of stress and frustration for parents and caregivers. While numerous factors have been associated with sleep disturbances, the chronobiology connection to sleep disturbances in children is virtually unknown to health care providers and parents. Facilitating the entrainment of a child's circadian rhythms, specifically melatonin is an easy and cost effective solution that may serve to alleviate sleep problems.

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