Editorial: Age-Related Decreases in Melatonin Secretion—Clinical Consequences

Pineal glands of humans and other mammals secrete melatonin at nighttime, thereby generating the now familiar circadian rhythms in plasma and urinary melatonin levels (1). But, although the hormone’s plasma levels at nighttime remain at least an order of magnitude higher than at daytime throughout the life span, its absolute concentrations undergo a continuing decline after peaking at ages 2–5 yr (2–4). This decline could be related to the failure of the pineal—unlike the pituitary—to grow, to its still unexplained tendency to calcify, or to even to effects of other age-dependent hormones on pineal cells or their neural inputs. The reductions in nocturnal plasma melatonin that occur around pubescence could be a factor in causing the sexual maturation, if melatonin is an endogenous gonad-inhibitor in people as it is in some laboratory rodents. However, the evidence for such an antogonadal effect is minimal. In contrast, compelling evidence is available that the reductions that occur later in life do have a clinically relevant consequence (i.e. the insomnia observed in at least some of the older people who suffer from this condition): normal sleep can often be restored by administering doses of the hormone that raise nighttime plasma melatonin levels to what they were earlier in adult life (i.e. 100–200 pg/mL) (4, 5, 5a).

It had previously been proposed that the decline in melatonin secretion observed toward the end of the first decade of life depends not on the individual’s age per se but on his or her pubertal stage (2). Now, Salti et al. (6), describing findings on eight male and eight female subjects, aged 8.7–16.8 yr, confirm that it is pubertal stage and not chronologic age that counts. They also describe ultradian melatonin cycles, with periods of 3.4 and 1.5 h, in their pubescent subjects. It cannot now be stated whether the puberty-associated decline in plasma melatonin has endocrine consequences, or whether it is simply a response to the other endocrine changes occurring concurrently, or perhaps a temporally coincident, but otherwise unrelated, phenomenon. No data are available as to whether administering melatonin in the midst of pubescence would alter its course, nor, obviously, would it be ethical to conduct such an experiment. Moreover, changes in plasma melatonin levels within their normal dynamic range have not been shown to affect any other hormones in humans.

What other consequences might arise from the declines in nocturnal plasma melatonin levels that occur with pubescence and at other particular ages? To answer this question one might consider what effects are now known to follow the administration of physiologic oral doses of the hormone (usually about 0.3 mg, depending on the fillers also present in the pill or capsule) when the plasma levels are in their low daytime range.

Two such effects have been well characterized: phase shifts in the timing of certain circadian rhythms (7) and the induction or maintenance of normal sleep (8). Although it is not established—contrary to the probable laments of readers who find it progressively more difficult to accommodate to eastbound overnight flights—that the ability to sustain or shift circadian rhythms varies with one’s age, there is considerable anecdotal evidence and some supporting laboratory data, suggesting that the depth of sleep declines early in adolescence, when nighttime plasma melatonin levels are falling, as in the subjects of Salti et al. (6).

Moreover, there is overwhelming evidence that sleep quality undergoes clinically relevant deterioration in many older people, manifest either as an increase in sleep latency or, more commonly, as more frequent and longer-lasting nocturnal awakenings. (That nocturnal plasma melatonin levels do, indeed, decline markedly in most people by the sixth or seventh decades of life has been demonstrated in all but one of the twenty-odd laboratories that have written on this subject. It should be noted that, to our knowledge, no adequate longitudinal data are available, tracing individuals’ plasma melatonin cycles over several decades. Thus, we must rely, as Salti et al. (6) have done, on comparisons of groups of older and younger subjects.)

What is the evidence that an age-related “melatonin deficiency state” promotes insomnia in some older people and that this insomnia can be treated with doses of melatonin that restore the amplitude of the plasma melatonin rhythm to that seen in young adults? In an initial study (5), nine elderly insomniac subjects who received melatonin (0.3 mg) 30 min before bedtime demonstrated significant increases in sleep efficiency (the percentage of the time in bed when subjects actually slept) and significant decreases in nocturnal awakenings and in sleep latency (the number of minutes between the time the subject went to bed and the time he or she fell asleep). In a more recent, larger study (5a), two groups of 15 older subjects, with and without actigraphically-confirmed insomnia, received a placebo or each of three melatonin doses (0.1, 0.3, or 3.0 mg) for 7-day periods, followed by 7-day washout periods. Once again, the hormone corrected the depressed sleep efficiencies of the insomniacs; moreover, the physiologic dose (0.3 mg) was significantly more effective than either the higher or lower doses in producing this desired effect.

Interestingly, the hormone had no discernable effect on sleep among the noninsomniac subjects, even though those subjects, like the insomniacs, had nighttime plasma melatonin levels that were well below those seen in younger adults: apparently, the age-related decline in nocturnal plasma mel-
atonin is not sufficient, in itself, to cause insomnia in all subjects. However, those who do manifest this symptom can be effectively treated by correcting that decline. Similar observations on the anti-insomnia effects of physiologic doses of melatonin have been described by numerous other investigators (e.g. Ref. 9). Such doses apparently do not shift circadian rhythms if they are administered at the subject’s normal bedtime hour; moreover, unlike higher doses, they also do not cause hypothermia (8). Melatonin also promotes sleep in young people with normal melatonin rhythms, if administered at a time of day (e.g. 1200–1800 h) when plasma melatonin levels are low (8).

Few data are available on the use of supplemental melatonin to promote sleep in normal children, however, the hormone has been used with some success in treating neurological disorders (like Angelman’s syndrome and Rett’s syndrome), which are characterized by severe insomnia (compare Refs. 10 and 11). Especially in dealing with such chronic diseases, physicians should endeavor to use the lowest effective melatonin dose, lest the hormone stop working because of receptor down-regulation, or that it have unrecognized subtle side effects when given chronically.

Finally, melatonin has in the past few years been shown to produce a wide array of biochemical and pharmacological effects. Even though most of these have required concentrations of the hormone that clearly exceed those present in blood or cerebrospinal fluid, some apparently do occur at physiologic levels and might, thus, occur in vivo and be affected by the declines in melatonin availability that are associated with pubescence or aging. And even those effects that require heroic doses could, because of the hormone’s unusually low toxicity, underlie possible uses of melatonin to treat related diseases. All that is needed are some compelling clinical data.

Richard J. Wurtman
Clinical Research Center
Massachusetts Institute of Technology
Cambridge, Massachusetts 02139

References