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Age-Related Sleep Disruption and Reduction in the Circadian Rhythm of Urine Output: Contribution to Nocturia?

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Abstract

Aging is associated with a marked increase in sleep complaints, and one factor causing sleep disruption is waking to void (nocturia). Urological surveys have found that few young adults report nocturia symptoms, but about half of those in their 60's and nearly 80% of older age groups are affected. Sleep surveys have found nocturia is a major cause of sleep disruption, with a majority of older adults with sleep disruption citing the need to void as the cause of their awakening. While much of the urological literature implies that nocturia causes sleep disruption, age-related changes in sleep depth and continuity may make it more likely that an older adult will wake in response to a filling bladder, or that an older adult will wake for another reason and then decide to void. There is also evidence that age-related changes in the amplitude of circadian rhythms contribute to nocturia. There is a well-described circadian rhythm in urine output, and evidence of circadian rhythmicity in some diuretic and anti-diuretic hormones. In this article we describe how age-related changes in sleep depth and continuity and age-related changes in circadian rhythm amplitude may contribute to nocturia, and how nocturia in turn leads to sleep disruption. Better understanding of how changes in sleep and circadian rhythmicity impact nocturia may lead to improved treatments and better quality of life for older adults.

Keywords

Aldosterone; circadian; nocturia; obstructive sleep apnea; sleep; vasopressin

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CONFLICT OF INTEREST

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1. INTRODUCTION

Nocturia is a common cause of sleep disruption in older people (1). While once thought to primarily affect men and to be caused by benign prostatic hypertrophy, nocturia is now considered to be a non-gender-specific problem. Several urological survey studies have examined self-reports of nocturia in different age groups, and all found that while few (<5%) young adults report nocturia symptoms, about half of those in their 60's report nocturia, with some reports that nearly 80% of the oldest age groups are affected (2–6). In sleep surveys where specific questions are asked (7–9), nocturia is reported to be a major cause of sleep disruption, and is significantly associated with daytime sleepiness (9, 10).

There are several known causes of nocturia (outlined below), but often when those potential causes of nocturia are treated, the nocturia persists. For example, nocturia in older men is assumed to be caused in most cases by benign prostate hypertrophy (BPH). However, both surgical and medical treatments of BPH often fail to resolve the nocturia (11–13) (11, 12, 14, 15), arguing that BPH was not the (only) cause of the nocturia. In addition, nocturia is just as prevalent among older women as older men (2, 16), and treatments for overactive bladder (OAB) often also fail to resolve nocturia. Many medications prescribed to older adults can contribute to nocturia, with diuretics the most obvious of these. In patients with normal daytime bladder capacity and no outflow obstruction, and in whom medication- and non-urological medically-related causes of nocturia have been ruled out, a “decreased nocturnal bladder capacity” is often cited as the cause of nocturia. However, in most such patients it is unknown what has caused the decreased nocturnal bladder capacity, and one study failed to find any relationship between a urological diagnosis and nocturnal bladder capacity (17, 18). One possibility is that there is a day-night change in bladder capacity that occurs with aging in some patients, although there is no evidence to support this. Nocturnal polyuria (an increase in urine production at night) is cited as the cause of decreased nocturnal bladder capacity in many such patients. The underlying cause of this increased nighttime urine production is thought to be due to changes in the circadian rhythm of hormone(s) involved in fluid and electrolyte balance. However, few of those studies controlled for day- night or age-related differences in posture, sleep, or fluid intake, making interpretation of those findings difficult.

In addition to other known causes of nocturia, we also believe that many older people have nocturia because of typical age-related changes in sleep depth and continuity. In such patients, we believe that the patient wakes during the night because of decreased sleep depth and chooses to void, thereby giving the appearance of decreased nocturnal bladder capacity.

2. NOCTURIA

While the recent consensus definition of nocturia is waking one or more times during the night to void (19, 20), older reports in the urological literature have often applied a stricter definition of nocturia (requiring >1 void per night to meet the criteria of nocturia). Voiding in the night was traditionally seen as a male problem caused by benign prostate hypertrophy (BPH), that nocturia is the least specific symptom of BPH, and although it is now recognized that women experience similar urges to urinate at night, and nocturia is now

considered to be a non-gender specific problem (16, 21). Nocturia is thought to result from nocturnal urine output exceeding maximal bladder capacity. From this, three broad pathophysiologies can be inferred for the generation of nocturia: 1) decreased functional bladder capacity; 2) excess production of urine at night (nocturnal polyuria); or 3) a combination of both (17).

Nocturnal polyuria has been defined as an increased urinary output during the night but, in contrast to diabetes insipidus, the 24-h urine production does not increase, indicating a modification in the normal diurnal production of urine (22). The standardization subcommittee of the International Continence Society recommends using a frequency-volume chart to help discriminate the three etiologies of pure nocturia (id est: without daytime polyuria) (17, 19, 23). A study has shown that 7% of the population with nocturia have isolated nocturnal polyuria, 57% have decreased functional bladder capacity, and 36% a combination of both (23).

2.1 Nocturia and aging

Nocturia is defined differently in various reports as “1 or more” or “2 or more” voids per night, and is a common cause of sleep disruption in older people (1). Several urological survey studies have examined self-reports of nocturia in different age groups, with some reports that nearly 80% of the oldest group affected (2, 3, 24). A study in Austria by Schatzl et al. found that while 3% of adults younger than 30 years of age reported nocturia symptoms (two or more voids per night), this increased to 30% of those aged 60–69, and to 40% of those aged 70 and older (4). In another study, the prevalence of nocturia in men was reported to be 16% when aged 40–49, increasing to 55% in those older than 70 [using a definition of 2 or more voids per night] (5). In a study by Middelkoop et al., the prevalence of nocturia (2 or more voids per night) was 66 and 58% respectively in men and women aged 50–59 years (2). A more recent study from the Netherlands using the current consensus definition of nocturia as one or more voids per night (19, 20), reported that 62% of men aged 55–74 and 80% of men over age 75 experienced nocturia, with similar rates in women (6).

In sleep surveys, nocturia is similarly reported to be a major cause of sleep disruption. The 2003 National Sleep Foundation “Sleep in America” poll of more than 1400 American adults over the age of 55 found that nocturia was the most common factor related to disrupted sleep (7, 8). Over half of the respondents with disrupted sleep (53%) reported waking at night to void on a regular basis, and this was the second strongest predictor (after depression) for sleep disruption (7). After correcting for other medical conditions, nocturia presented a 75% increased risk of self-reported insomnia in the study respondents. In a survey study we conducted of middle-aged and older adults, we found a positive correlation between urological symptoms and sleep disruption (25). The Cardiovascular Health Study surveyed more than 4,000 people over age 65 about their daytime sleepiness and nighttime sleep quality. They found that 89% of the men and 86% of the women who reported awakening during the night cited the need to urinate as the cause of their awakening (9). Daytime sleepiness, as measured by the Epworth Sleepiness Scale, was significantly correlated with the cause of waking at night to void in both women and men in both the Cardiovascular Health Study and in the National Sleep Foundation Poll (9, 10). In our

survey study, we found that greater urological complaints were also associated with greater levels of self-reported daytime sleepiness (25).

These studies and surveys suggest that nocturia is a common feature of aging. As described in greater detail below, there are several known causes of nocturia, although often when those potential causes of nocturia are treated the nocturia often persists (11–13). We believe that age-related changes in sleep depth and continuity, and age-related changes in circadian rhythms related to fluid and electrolyte balance and urine production are an under-appreciated cause of nocturia.

2.2 Decreased functional bladder capacity as a cause of nocturia

One of the factors that can contribute to an increase in the frequency of nocturnal urination is a reduced functional bladder capacity. Using a frequency-volume chart, Homma et al. documented that the average bladder capacity went from 256 mL to 152 mL in men as they age, and from 202 mL to 111 mL in women (26). The average frequency of nocturnal voids went from 0.5 in the younger to 1.8 in the 80–89 year-old group in men, and from 0.7 to 1.7 in women for the same age groups. Diminished functional bladder capacity can be caused by a variety of factors, including bladder obstruction, over activity, sensory urgency, inflammation, or malignancy. Awakening from sleep as a result of nocturia is thought to be secondary to the bladder stretch response, defined as the sensation of urinary urgency resulting from an overextended bladder. However, using the Nocturnal Bladder Capacity index (calculated from the frequency-volume chart by subtracting the predicted number of nocturnal voids from the actual number of nocturnal voids), Weiss and colleagues found no relationship between specific urodynamic diagnoses and the Nocturnal Bladder Capacity index (17, 18). This finding suggests that rather than awakening due to a filled bladder, patients first awoke due to a primary sleep disturbance, then proceeded to nighttime micturition. We have data (see below) demonstrating that healthy older people wake fewer times to void when sleeping under high sleep pressure, consistent with the idea that many nighttime voids are not due to bladder overactivity, but instead are due to a change in sleep.

2.3 Day-night variation in urine output

Urinary output by the kidney is influenced by both water and sodium balance. Diminished output of urine by the kidney is achieved either through urine concentration via water reabsorption or through sodium retention. In healthy young people, nighttime urine output is lower than daytime output (27), and early studies found that posture plays a role in this day-night variation. A study conducted by Thomas et al. in 1957 showed that going from the recumbent to the standing position was immediately followed by a decrease in urinary, sodium, and chloride output, whereas lying down was followed by the opposite changes (28). A hormonal mechanism was inferred, which later proved to be the plasma renin-angiotensin-aldosterone system (RAAS) (29). The plasma renin-angiotensin pathway is sensitive to postural changes through the juxtaglomerular apparatus, and acts through aldosterone to induce significant sodium retention. Later studies found that aldosterone secretion is also influenced by ACTH secretion, which has a circadian rhythm (30). Studies conducted in the 1970's were the first to reveal that the day-night difference in urine output is not solely due to postural changes, but also due in part to an endogenous rhythm in urine

production. Mills et al. carefully controlled food and fluid intake and posture in young adults while measuring urine output across day and night. Even when inverting the daily sleep-wake (and associated posture and food intake) routine (with sleep occurring at midday and awake recumbent position occurring at midnight), urinary output remained lowest at midnight (28, 31). This decrease in urinary output was accompanied by urine concentration, showing there was an underlying circadian influence on the rhythm of urine output. Later studies revealed that vasopressin was the hormone involved in this response, and diurnal variations of vasopressin in healthy young adults parallel these variations in urinary output (32). Finally a third important natriuretic hormone, the atrial natriuretic peptide (ANP) has been shown to play an important role in sodium excretion at night (33).

A study by Kirkland and colleagues (27) was the first to show that healthy older people had a higher ratio of nocturnal urinary excretion than young adults (52% versus 25% in their study), even though the amount of sleep (7.22h and 7.25h respectively) and 24-h urinary output (about 1600mL) were similar in both groups. This finding has been reproduced in several other studies, including one we conducted. We studied 23 healthy older men and women and 26 healthy young men. After several baseline days and nights in the laboratory, each participant remained awake for 40 hours, sitting in bed, with food and fluid distributed evenly across day and night as hourly snacks, and had the timing and volume of each void documented. When we examined the amount of urine voided over the first 24 hours, we found no difference between the age groups (older: 2456.8 ± 535.2 mL, younger: 2288 ± 573.3 mL). However, the older participants had a significantly greater urine output during the 8 hours corresponding to their usual sleep time than the young participants (707.6 ± 365.0 vs. 364.7 ± 284.3 mL, $p < 0.01$), representing approximately 28% of their daily urine production compared with only 16% in the young adults.

The two main hormonal systems (vasopressin and renin-angiotensin-aldosterone) which influence urine output by the kidney have been the focus of subsequent studies seeking to understand the cause of the observed age-related changes in day-night urine output.

2.4 Hormonal regulation of urine output and effect of aging on these hormones

Vasopressin (AVP) is a water-conserving hormone that controls fluid balance, and it may play a role in the prevalence of nocturia. The circadian rhythm of urine output is thought to be established by the age of 5 years, at which time a greater proportion of urine is excreted during the day than at night. In young adults, vasopressin has been reported to exhibit a diurnal rhythm with a peak during the night time hours. In older people, the vasopressin rhythm has been reported to be missing or attenuated. Most studies have found a lack of nocturnal rise in AVP in older people, although most did not control for age-related differences in sleep (34, 35), nor did they screen for obstructive sleep apnea (OSA), which has been shown to suppress AVP (see below). There is also a report of a gender difference in AVP levels in aging, with older men having two-fold higher plasma AVP levels than older women (34). However, a study that compared vasopressin levels in older people with and without nocturnal polyuria found no difference in vasopressin levels (36), and when desmopressin (a synthetic replacement for vasopressin) is used as a treatment for nocturnal polyuria it shows a limiting effect and does not always treat the symptoms (37). Thus,

attenuation or abolishment of the vasopressin rhythm cannot fully explain the increased nocturnal output of urine in older people.

Atrial natriuretic peptide (ANP) causes renal sodium excretion and suppresses the release of AVP, decreases plasma renin activity, angiotensin II synthesis, and aldosterone secretion. Therefore, it may be another contributing factor to nocturia (38, 39). A report by Cugini et al. found that in 10 healthy older people, global ANP levels were significantly higher compared to those of younger people, but they were actually slightly lower during the night than during the daytime (38). Although the authors controlled posture and fluid and food intake, they did not control for sleep-specific effects on ANP, and given the prominent age-related changes in sleep it remains unclear whether the findings are due to differences in endogenous levels of ANP at night, or are due instead to differences in sleep. In patients with sleep apnea, more apnea events correlate with increased ANP secretion at night and in turn, increased ANP secretion at night has been associated with increased nocturnal urine output and nocturia (150).

The renin-angiotensin-aldosterone system (RAAS) has a role in the conservation of sodium in the kidneys via the action of aldosterone. There is evidence that this system is affected by age. Studies in healthy older people ages 62–70 with normal dietary salt intake showed that plasma renin activity and aldosterone in the supine position still displayed significant periodic 24-h oscillations; the levels of plasma renin were significantly lower when compared to young adults aged 20–30; the levels of cortisol (a reflection of ACTH activity) were also lower (statistically non significant); but aldosterone levels were higher in the older adults compared to the young (38). These contradictory results need to be verified in a study where not only posture, but also sleep itself is controlled. In another study, no difference in plasma renin and aldosterone levels between older men with nocturnal polyuria, older men with nocturia non-associated with nocturnal polyuria, and older men without nocturia was found (40). Thus, the role of the sleep-wake cycle in aldosterone secretion, and how age-related changes in sleep might affect aldosterone secretion (in turn affecting urine output), is not entirely clear.

Two well-designed studies in young subjects by the Brandenberger group demonstrated that day-night variations in aldosterone secretion are closely tied to the sleep-wake cycle, rather than being primarily under circadian control like cortisol. In the first study (41), young subjects were studied under normal conditions and again under 24-h sleep deprivation. They found that the well-known increase in aldosterone during the night was blunted during sleep deprivation, although levels were not lower during daytime hours when the sleep deprivation continued. Those results suggested that the nocturnal increase in aldosterone is due primarily to sleep, rather than due to an underlying circadian rhythm. In a second study (42), the authors also sleep deprived subjects, but then allowed them to sleep during the daytime. In that study, they found that aldosterone was at significantly higher levels during sleep compared to wake, regardless of whether the sleep occurred at night or was shifted to the day.

2.5 Nocturia and obstructive sleep apnea

Although prostate and bladder disorders clearly contribute to many cases of nocturia in older patients, there are other contributing factors to nocturia that need to be considered. Obstructive sleep apnea (OSA) is now recognized as contributing to nocturia (43, 44). Two mechanisms may be involved in the pathophysiology. First, the sleep fragmentation / disruption induced by OSA may lead to awakenings which are then followed by a decision to void, as described in the study by Pressman et al. (45). Second, OSA has also been shown to induce nocturnal polyuria through an increase in the circulating levels of the hormone ANP (150), which in turn leads to suppression of AVP and the renin-angiotensin-aldosterone system (46, 47). Furthermore, treatment of OSA with continuous positive air pressure has been demonstrated to reduce the number of nighttime voids (48). OSA is highly prevalent in middle-aged and older adults and is frequently undiagnosed (49). Therefore, OSA should be considered in the diagnosis and treatment of nocturia. OSA has also been demonstrated to be strongly associated with overactive bladder (153), which itself is associated with nocturia.

3. SLEEP AND AGING

It has long been recognized that sleep patterns change with age. A common feature of aging is the advance of the timing of sleep to earlier hours (50–56), often earlier than desired (57–59). The sleep of older people is also characterized by an increased number of awakenings (60) and a reduction of Stages 3 and 4 sleep (also called slow wave sleep, SWS, N3) (53, 61–80), the deeper stages of nonREM sleep. These age-related changes are also associated with sleep complaints. More than 50 years ago, McGhie and Russell (59) reported that 15% of older people suffer from early morning awakenings (defined as inability to sleep past 5 a.m.), a finding which has been confirmed by a number of survey studies carried out since that time (57). In a survey among general practice patients over age 65, 33% reported that they wake up too early in the morning at least a few times a week (58), and occasional problems sleeping are reported by about 40% of the older population (7, 81).

This may explain the increase in the use of sleep medications with age (75, 82), and the increased daytime sleepiness reported by many older people (51, 71, 83, 84). In fact, the 2003 National Sleep Foundation “Sleep in America” poll found that 15% of people over age 55 said they have daytime sleepiness so severe that it interferes with their daytime activities a few days a week, and an additional 12% reported suffering from severe daytime sleepiness several days per month (7). That same survey found that 27% of the respondents aged 55–64 reported driving a car while sleepy in the previous year, 8% reported actually falling asleep at the wheel, and 1% reported having a traffic accident after falling asleep while driving (85). Thus, in addition to affecting quality-of-life, age-related difficulties with sleep have important safety consequences, both for the affected individual and for society at large.

3.1 Changes in homeostatic sleep regulation with age

Sleep homeostasis refers to a putative mechanism by which the brain regulates the physiological drive for sleep. The term sleep homeostasis is used to refer to both a specific functional and a specific mechanistic aspect of sleep regulation. It implies that some

physiologic process maintains a cumulative record of and compensates for variations in the duration and/or quality of sleep. There is evidence that sleep EEG slow waves provide a measure of sleep intensity and the physiological drive for sleep ("sleep pressure"). A homeostatic regulation of nonREM Stages 3 and 4 sleep (slow wave sleep, SWS, N3) is observed during total sleep deprivation studies, and dose-response relationships between the duration of wakefulness and SWS have been established over a range of wake durations (86, 87). One neurophysiologic measure regulated by a homeostatic process is EEG power density in the 0.75–4.5 Hz range (delta frequency range, also known as slow-wave activity, SWA) measured in nonREM sleep. Delta frequency activity is a major component of the definition of SWS, but variations in SWA can be more easily quantified than changes in the number of minutes of SWS. In humans, SWA increases when wakefulness prior to sleep is varied from 2 to 40 hours (86, 88–91). The dose-response relationship between prior wake duration and SWA can be described by exponential saturating functions in young adults.

While these relationships have not been studied as extensively in older individuals, there is evidence of a dose-response relationship between wake duration and subsequent SWA, albeit at a different level. Manipulation of the sleep homeostat in older people has demonstrated that by extending the time awake preceding sleep from 16 h (normal waking episode length) to 40 h (after a night and day of total sleep deprivation), older people can attain higher sleep efficiency. Following this extension of wakefulness, there is an increase of slow wave sleep and EEG SWA in older people, although the levels of SWA after 40 h awake approached those of young subjects after only 16 h awake (78). These data suggest that in older people living on a normal sleep-wake schedule, the homeostatic drive for sleep that builds up during wakefulness is reduced compared with that in younger adults.

3.2 Nocturia and sleep

The age-related sleep homeostatic changes described above may represent one cause of the increased prevalence of nocturia observed with aging. Lighter sleep is associated with a greater propensity to awaken to environmental stimuli (92). Because older people spend less of their sleep time in the deeper stages of sleep, they are also more likely to be awakened by signals from the stretch receptors in the wall of the bladder that a young adult might sleep through. Supporting this idea is a study by Sugaya et al. that found that older individuals treated with hypnotic (sleep) medication or melatonin had a reduced number of voids during the night when compared to controls (151). Bliwise and colleagues reported that among a small group of middle-aged adults with nocturia, those who had more N3 sleep tended to wake fewer times to void (1–2) compared with those individuals who showed lower amounts of N3 sleep (who woke 3 or more times to void) (152). It may also be the case that due to age-related changes in sleep depth and continuity, any other stimulus (such as light or noise) that triggers an awakening may in turn lead the person to become 'aware' of their bladder and then 'decide' to empty it. We have preliminary data from our laboratory that are consistent with the idea that age-related changes in sleep depth and consolidation contribute to nocturia (93). We measured the number of awakenings to void during an 8-h baseline night (following a normal 16-h wake episode) with that from an 8-h high sleep pressure night (following 40 h awake) in 23 healthy (non-obese, with no acute or chronic medical conditions, no medications) older men and women. We found a trend for the participants to

wake fewer times to void on the high sleep pressure night (0.7 ± 0.9 vs. 1.3 ± 1.1 voids, $p=0.08$) when their sleep was deeper than during the baseline night.

Regardless of the cause of nocturia, it can reduce sleep duration and consolidation, leading to impaired alertness during the day. As survey studies have found, there is a high correlation between the self-report of waking during the night to void with symptoms of excessive daytime sleepiness (9, 10, 25). Nocturia can also lead to other medical problems, due to the increased risk of injury from falling at night (94, 95), depressive symptoms (96) and major depression (97, 98), and problems with memory consolidation. There are even reports that survival rates are lower in individuals with nocturia (99, 100). We believe that additional studies that explore the interplay between age-related changes in sleep depth and consolidation and nocturia are warranted to understand the causal relationships and to develop non-urolological treatments for nocturia.

4. HUMAN CIRCADIAN RHYTHMICITY

Daily oscillations with a near-24-h (i.e., circadian) period have been identified in nearly every organism studied, including humans. In mammals, the suprachiasmatic nuclei (SCN) in the hypothalamus act as the central pacemaker for the coordination of circadian rhythms in physiology and behavior (101–110). The human brain contains the same key structural elements as that of other mammals (111–115), and in fact the anterior hypothalamus was recognized as an important regulatory area for sleep-wake function as early as the 1920's (116–118), long before the SCN was identified (116).

Many peripheral tissues also exhibit circadian rhythms, with a unique subset of about 10% of the genes being clock-controlled in each organ (119, 120). Individual SCN neurons (121) as well as cells in the periphery (122–129) express endogenous circadian rhythmicity; under normal conditions the cells within an organ are synchronized with each other and with the activity of the whole organism (internal synchronization) by regular exposure to a 24-h light-dark cycle (103, 111, 130–133) and proper timing of the fasting-feeding cycle with respect to that light-dark cycle (external synchronization). Several papers have shown that in rodents, clock genes (*Bmal1*, *Clock*, *Cry1*, *Cry2*, *Per1*, *Per2*, *Rev-Erb1 α*) as well as fluid balance-controlling genes such as *ENaC* or *AVPR2* have a circadian expression in the kidney. Those fluid balance-controlling genes have been shown to be under the control of clock genes themselves, and altering the expression of those clock genes leads to disruption in the circadian rhythms of urine output and blood pressure (134, 135).

4.1 Changes in circadian rhythm amplitude with age

There is evidence from both animal and clinical studies that the amplitude of some circadian rhythms is reduced with aging (136–144). This has been hypothesized to arise from a reduction in the strength of the output signals from the SCN or a reduction of the coupling between the SCN and peripheral organs or tissues. While not all circadian rhythms show amplitude reductions with age, and among the rhythms that do change with age not all individuals are affected (145, 146), we hypothesize that a reduced amplitude of the circadian rhythm of urine output may contribute to the age-related increase in nocturia. As described in section 2.3 above, we and others have found that the day-night rhythm in urine output is

altered in aging, such that while 24-h urine production is similar between young and older adults, the amount produced at night is significantly greater in older adults. In a circadian rhythm study we conducted, we controlled the posture, sleep-wake state, environment, and food and fluid intake of a group of 26 healthy young men and 23 healthy older men and women (93). Each person remained awake, sitting in bed, received a small snack each hour (with identical amounts of calories, sodium, potassium, and fluids in each snack), and had the timing and volume of each void recorded. This design is to eliminate any external diurnal variations which could affect salt or water excretion by the kidney, such as changes in blood pressure induced by changes in posture, changes in salt intake due to individual preferences/ large meals, or changes in water intake, and ensure that we only see endogenous variations in urine output (as in variations regulated by endogenous circadian mechanisms).

We then calculated the rate of urine production across the 40-h study. When we examined the urine production of the two age groups, we found that while overall 24-h levels were similar, the older group produced more urine during the nighttime hours than did the young group (see Figure 1). We hypothesize that this reduction in amplitude of the circadian rhythm of urine output with aging contributes to nocturia in otherwise healthy older adults by causing more urine to be produced during the nighttime hours than in young adults. As outlined in section 2.4 above, there is some evidence that hormonal rhythms involved in fluid and electrolyte balance are altered with aging. However, circadian rhythm studies with carefully screened young and older participants need to be carried out to determine which hormonal rhythms are altered with aging.

5. NOCTURIA AND QUALITY OF LIFE

As outlined in the National Institute on Aging Strategic Plan, one of the challenges for the 21st century will be to take advantage of the increase in longevity that occurred during the 20th century by ensuring that older people are as healthy and productive as possible. “Lifestyle issues” can have an important impact on whether individuals age successfully or not, and obtaining sufficient sleep is one such lifestyle issue that has been largely ignored by society at large, as well as by much of the medical community. As the 2003 National Sleep Foundation “Sleep in America” poll found, more than half of adults over age 55 with a self-report of disrupted sleep report waking at night to void on a regular basis (8), and waking to void is in turn associated with daytime sleepiness and napping (9, 10, 25). In several survey studies, nocturia has been shown to be strongly associated with sleep disruption, self-defined insomnia, and daytime sleepiness. Nocturia also has important consequences for well-being and quality of life (4, 147, 148) and improvements in nocturia have been demonstrated to improve quality of life measures (149).

It is clear that the sleep disruption associated with nocturia that many older adults experience has significant impacts on their safety, health, and quality of life, as well as their ability to remain vital and productive members of society. Between 2000 and 2030 the number of Americans over age 65 is expected to double to more than 70 million, representing 20% of the US population (NIA Strategic Plan for 2001–2005), and the world population of those 65 and older is projected to grow from an estimated 524 million in 2010

to nearly 1.5 billion in 2050. A majority of this aging population will experience nocturia, and our current understanding of the pathophysiology of this disorder has significant gaps. Thus, multi-disciplinary research incorporating state-of-the-art experimental techniques in urology, chronobiology, endocrinology, and sleep medicine is required to understand the contribution of age-related changes in the amplitude of hormonal circadian rhythms and age-related changes in sleep quality to nocturia so that improved treatments can be designed to improve the health and quality of life of older adults.

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Figure 1. Urine output as a function of time in healthy young (black line) and older (red line) adults studied in constant conditions. Dashed vertical lines represent the time of the usual nocturnal sleep episode. Each participant remained awake, in a semi-recumbent posture, and received equal hourly aliquots of food and fluid for 40h, beginning at their usual wake time (reference clock hour = 8).