SESSION III: SPONTANEOUS GROWTH HORMONE SECRETION AND THE DIAGNOSIS OF GROWTH HORMONE DEFICIENCY

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Physiology of growth hormone secretion during sleep

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The temporal relation between the first few hours of sleep and the secretion of growth hormone (GH), which is present in normal persons of both sexes from early childhood until late adulthood, is reviewed. In adults the most reproducible pulse of GH secretion occurs shortly after the onset of sleep in association with the first phase of slow-wave sleep (SWS) (stages III and IV). In men approximately 70% of the GH pulses during sleep coincide with SWS, and the amount of GH secreted during these pulses correlates with the concurrent amount of SWS. Sleep-related secretion of GH appears to be primarily dependent on the release of growth hormone-releasing hormone. Rodent and human studies have shown that growth hormone-releasing hormone injections decrease wakefulness and increase SWS. During the fourth decade of life (ages 30 to 40 years) the total amount of GH secreted over a 24-hour span decreases by two- to threefold. Similarly, the amount of SWS decreases dramatically over the same narrow age range. Because the sleep-onset GH pulse is often the major secretory output in adults, age-related decrements in sleep-related GH secretion likely play a major role in the hyposomatotropism of senescence. (J Pediatr 1996;128:S32-7)

The 24-hour profile of plasma growth hormone levels in normal adults consists of stable low levels interrupted by bursts of secretion. The most reproducible pulse occurs shortly after the onset of sleep in association with the first phase of slow-wave sleep.[1] In men the sleep-onset GH pulse is generally the largest and often the only pulse observed over the 24-hour span. This is well illustrated by the mean 24-hour GH profile in eight normal young men ranging in age from 20 to 30 years shown in Fig. 1.[2] In women daytime GH pulses are more frequent, and the sleep-associated pulse, although still present in most cases, does not generally account for the greater part of the 24-hour release of GH.

The onset of sleep will elicit a pulse in GH secretion whether the sleep is advanced, delayed, or interrupted and reinitiated.[3] After the onset of normal nocturnal sleep, slow-wave activity consistently precedes the elevation in plasma GH levels. A study with blood sampling at 30-second intervals during sleep has shown that maximal release of GH occurs within minutes after the onset of SWS.[4] Some studies have suggested that it is the onset of sleep itself rather than the occurrence of SWS that is the primary determinant of sleep-related GH secretion. Pulses of GH may indeed be ob-

GH	Growth hormone
GHRH	Growth hormone-releasing hormone
REM	Rapid eye movement
SWS	Slow-wave sleep

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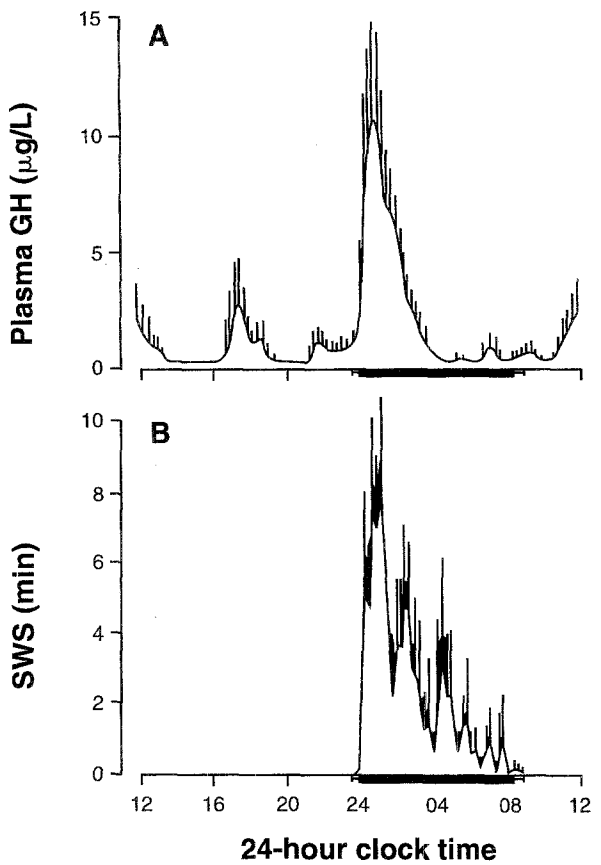

Fig. 1. Mean (SEM) 24-hour profiles of plasma GH levels (**A**) and amounts of SWS (**B**) in each 15-minute interval between blood samplings in eight normal young men. *Black bars* indicate sleep period. (From van Coevorden A, et al. Neuroendocrine rhythms and sleep in aging. Am J Physiol 1991;260:E651-61.)

served after the onset of sleep in the absence of stages III and IV. Nevertheless in studies that have investigated the secretion of GH in normal young men of similar height and weight, it has been found that approximately 70% of the GH pulses during sleep correlate with the SWS stages.[3] Furthermore, increase in SWS, as occurs after sleep deprivation[5] or pharmacologic treatment, results in a marked increase in the concurrent secretion of GH, supporting a causal relation between SWS and GH release.

The relation between sleep stages and GH release is more apparent when GH secretion rates rather than peripheral concentrations are examined. This is illustrated in Fig. 2, in which the association between pulsatile GH secretion and sleep stages was studied in a single subject.[3, 6] The profile in Fig. 2, *A*, is the plasma levels of GH measured at 15-minute intervals. Three pulses of plasma GH levels were detectable with a computerized pulse-detection algorithm. The corresponding profile of GH secretion rates calculated by decon-

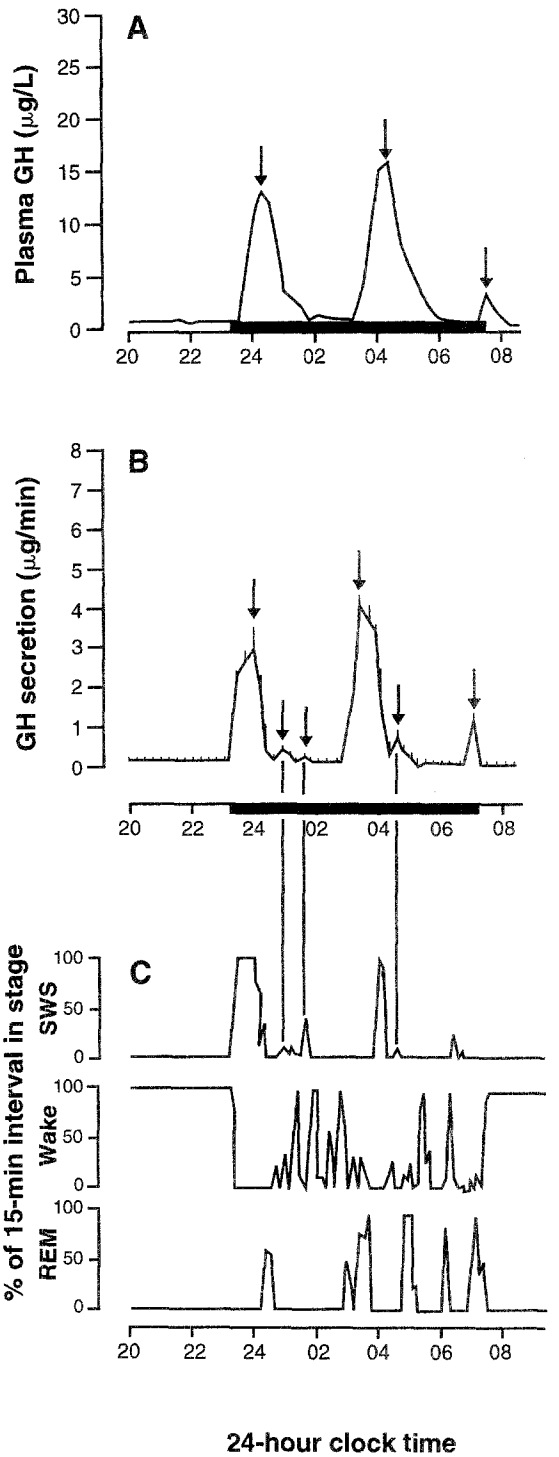

Fig. 2. Twenty-four-hour profiles of plasma GH levels (**A**), mathematically derived GH secretion rates (**B**), and sleep stages (**C**) in normal young man during polygraphically recorded sleep. *Black bars* indicate sleep periods. Measurable pulses of plasma GH levels and GH secretion rates are indicated by *arrows*. (From Van Cauter E. Computer-assisted analysis of endocrine rhythms. In: Rodbard D, Forti G, editors. Computers in endocrinology. New York: Raven Press, 1990:59-70.)

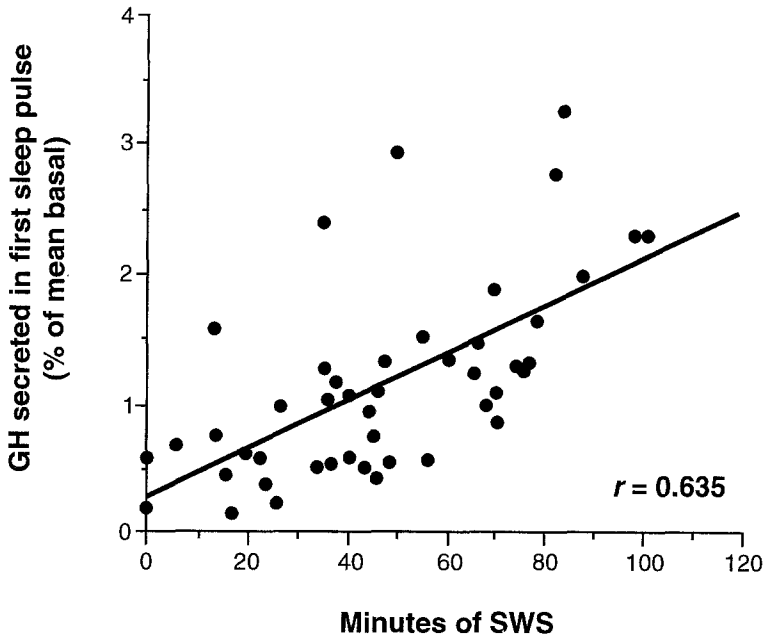

Fig. 3. Relationship between amount of GH secreted and amount of SWS in sleep-onset GH pulses in normal young men. (Data from Van Cauter E, et al. J Clin Endocrinol Metab 1992;74:1441-50.)

volution is shown in Fig. 2, *B*. These rates were derived from the plasma levels with a mathematic model for GH disappearance that assumed a single compartment. As seen in Fig. 2, *B*, pulse analysis of the secretion rates shows the occurrence of three additional pulses of GH secretion. The percentages of each 15-minute interval between blood samplings that were spent in stages wake, SWS (stages III and IV), and rapid eye movement are shown in Fig. 2, *C*. By comparing the profiles of GH plasma levels and SWS, it can be seen that the sleep-onset pulse of GH that occurred concurrent with the first SWS period spanned the first 3 hours of sleep without apparent modulation by the succession of wake and REM stages. However, the profile of the secretion rates clearly shows that GH was preferentially secreted during SWS with interruptions in secretion coinciding with the intervening REM or wake stages. Thus deconvolution showed a closer association between SWS and active GH secretion than the analysis of plasma concentrations, because the temporal limits of each pulse were more accurately defined, and additional pulses were revealed. This pulse-by-pulse analysis of the nocturnal profiles of GH secretion rates shows that the amount of GH secreted in SWS-associated pulses correlates with the amount of SWS occurring during the pulse (Fig. 3).[3]

Although SWS is a major determinant of the 24-hour GH profile, evidence for the existence of a circadian modulation, i.e., an intrinsic effect of the time of day, also exists. In a study in which the nocturnal profile of GH was observed after a 5-hour delay in bedtimes,[3] a GH pulse occurred during wakefulness within 1 hour after the usual bedtime on 12 of 16 nights. It is possible that ultrasensitive GH assays will show the existence of a sleep-independent circadian rhythm of GH release.

PUTATIVE MECHANISMS LINKING SLEEP AND GH SECRETION

Various studies have indicated that cholinergic pathways are involved in controlling GH release including sleep-related GH release in response to various stimuli.[7-9] Furthermore this cholinergic control is effected through the regulation of hypothalamic somatostatin release. Thus it appears that sleep-onset secretion of GH occurs during a period of relative somatostatin withdrawal. In addition, evidence exists that sleep-onset release of GH is regulated by growth hormone-releasing hormone stimulation.[10] Indeed, factors that inhibit GH secretion by increasing somatostatin inhibition such as hyperglycemia or GH autofeedback do not suppress the sleep-onset pulse of GH. In contrast, awakenings during ongoing secretion of GH immediately inhibit further release, as shown by the nocturnal profiles of plasma GH, GH secretion rates, and sleep stages in Fig. 4.[11]

Conversely, the effects of GHRH on sleep have been demonstrated, and it has been suggested that GH secretion and sleep may share common regulatory mechanisms.[12] Intracerebroventricular injections of GHRH in rats and rabbits increase both REM and non-REM sleep.[13, 14] Inhibition of endogenous GHRH either by the administration of a competitive antagonist or by immunoneutralization inhibits

sleep.[12] Several studies have shown that the administration of GHRH during sleep may decrease the amount of wake time and increase the amount of SWS.[15, 16] These somnogenic effects of GHRH could be mediated by GH, but this hypothesis is not supported by the finding of a significant decrease in stage III sleep after GH therapy in GH-deficient children.[17] Supporting the link between activity of the somatotropic axis and sleep regulation is the observation that the power of SWS in subjects with congenital isolated GH deficiency is significantly less than that in normal patients in a control group.[18] The association of increased GH secretion with an increased need for sleep in adolescents is also consistent with there being a functional relation between GH secretion and sleep. Short stature and poor weight gain have been described in children with obstructive sleep apnea, and therapeutic tracheostomy may lead to a sustained increase in their growth rate.[19] The nocturnal secretion of GH is decreased in adults with sleep apnea, and treatment with positive airway pressure restores sleep-onset secretion of GH.[20, 21]

ALTERATIONS IN SLEEP-RELATED GH SECRETION DURING SEXUAL MATURATION AND AGING

The total amount and the temporal distribution of GH release are strongly dependent on age. Spontaneous secretion of GH is detectable in term infants who appear to have a high level of tonic secretion.[22] As an infant matures, the frequency and amplitude of the GH pulses decrease, and tonic secretion diminishes.[22] A pulsatile pattern of GH release with increased amplitudes during sleep is present in prepubertal boys and girls.[23] During puberty the amplitude but not the frequency of the pulses is increased, particularly at night.[24, 25] Maximal overall GH concentrations are reached in early puberty in girls and in late puberty in boys.[25] The 24-hour GH profiles in sexually mature 16-year-old boys and in young men in their late 20s and early 30s are illustrated in Fig. 5.

Age-related decreases in GH secretion have been well documented in both men and women.[2, 26] The amount of GH secreted daily in healthy men older than 65 years of age is generally less than one third that in men younger than 30 years.[2, 27] The amount of SWS in older adults is similarly drastically reduced. This decline in overall GH secretion appears to be caused primarily by a decrease in pulse amplitude rather than frequency. In a recent retrospective analysis[28] we showed that these dramatic effects of aging on SWS and GH secretion occur early in adulthood and are essentially complete by the end of the fourth decade of life. Early studies had generally concluded that sleep-related GH pulses are absent in the elderly, but more recent studies in elderly subjects uniformly show persistent but reduced GH secretion during sleep.[2, 27] In our analysis of more than 100 profiles of the plasma GH levels in men ranging in age from 18 to 82 years, it is apparent that the proportion of the daily GH output that occurs in the first few hours of sleep does not decrease with age but remains stable or even increases slightly. Basal GH secretion is higher in premenopausal women than

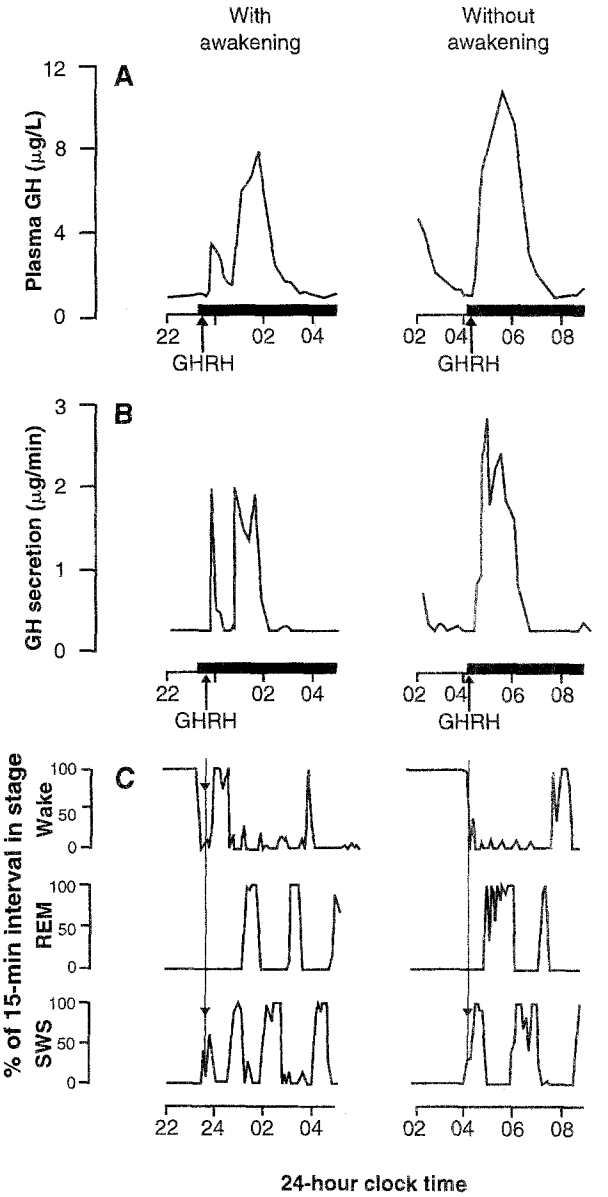

Fig. 4. Profiles of plasma GH levels **(A)**, GH secretion rates **(B)**, and sleep stages **(C)** in same subject after injection of 0.3 μg/kg GHRH *(arrows)* after 1 minute of SWS on two separate occasions. *Left panel*, subject spontaneously awoke during ongoing GH secretory response, and secretory process was abruptly interrupted. *Right panel*, subject remained asleep throughout secretory response. *Black bars* indicate sleep period. *Vertical arrows* indicate temporal coincidence of GH secretory pulses and SWS. (From Van Cauter E, Caufriez A, Kerkhofs M, Van Onderbergen A, Thorner MO, Copinschi G. Sleep, awakenings and IGF-I modulate the growth hormone secretory response to growth hormone–releasing hormone. J Clin Endocrinol Metab 1992;74:1451-9. © The Endocrine Society.)

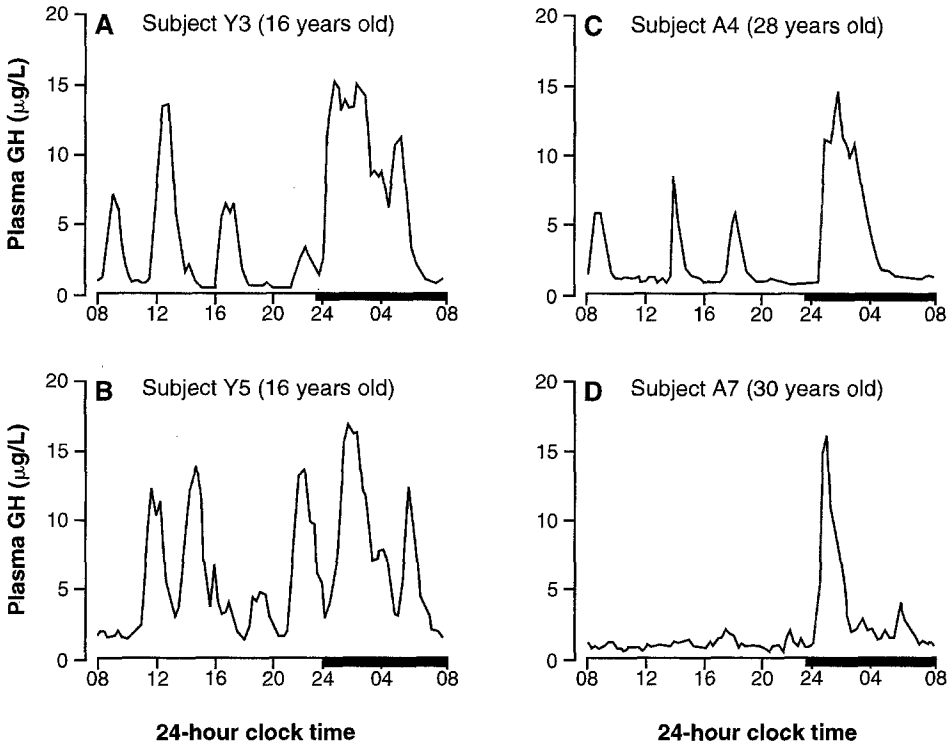

Fig. 5. Twenty-four-hour profiles of plasma GH levels in fully sexually mature adolescent boys (**A** and **B**) and in young men around end of third decade of life (**C** and **D**). *Black bars* indicate sleep period. Decrease in GH secretion during daytime and later part of sleep period in early adulthood is typical of age-related changes in 24-hour GH profile.

in age-matched men.[26] The daily output of GH in women correlates with their estradiol levels.[27] In old age these sex differences no longer exist.

SUMMARY

From early childhood until late adulthood the onset of sleep is a robust stimulus for GH secretion. Most GH pulses during sleep occur in temporal association with SWS. However, GH pulses during sleep may be observed in the absence of SWS, and in studies with standard assay procedures only one third of the SWS periods appear to be associated with detectable GH secretion. The absence of a one-to-one association between SWS and GH secretion is likely to reflect the dual control of GH pulsatility by both GHRH and somatostatin. Indeed, the sleep-onset pulse appears to result from pulsatile stimulation by GHRH that is concomitant with a relative withdrawal of inhibitory somatostatin tone. Other less consistent pulses may reflect GHRH stimulation in the absence of somatostatin withdrawal or conversely somatostatin withdrawal in the absence of GHRH stimulation. Evidence from studies with GHRH antagonists suggests that GHRH stimulation plays a more important role than somatostatin withdrawal in mediating the effects of SWS on GH secretion and that GHRH and sleep regulation may share common mechanisms. Age-related decreases in GH secretion and SWS occur in parallel, with both deficits being essentially complete by the end of the fourth decade of life. It appears therefore that strategies to restore youthful levels of somatotropic activity in adults may be more successful in midlife than in late life, when peripheral tissues have not been exposed to significant amounts of GH secretion for several decades.

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