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Higher Plasma IGF-1 Levels Are Associated With Increased Delta Sleep in Healthy Older Men

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Background. Sleep quality declines with age, with less time in deep or slow wave sleep (SWS) and reduced amplitude of the delta waves that characterize it. Age-related declines also occur in lean body mass, growth hormone (GH), and insulin-like growth factor 1 (IGF-1). These changes in sleep quality and anabolic status may be related, as administration of GH or growth hormone releasing hormone (GHRH) can enhance SWS and decrease awakenings in young men. Here we examine the relationship between plasma IGF levels and delta sleep quality in older men.

Methods. The sleep EEG of 30 healthy elderly men (64 ± 6 yrs; range 50–75) was recorded on the second of 2 consecutive nights. Plasma samples were drawn within 3 weeks of EEG recording, and IGF levels were assayed by RIA after acid extraction.

Results. IGF explained 28% (semi-partial correlation coefficient $r = .53$; $p = .003$) of the variance in average delta energy per epoch of SWS, after age-related variance was removed. Higher IGF was associated with higher average delta energy. Similar results were obtained for total delta energy during SWS ($r = .37$, $p = .04$) 4nd time spent in SWS ($r = .42$, $p = .02$). Other measures of sleep quality (e.g., wakefulness, REM sleep) were not correlated with IGF. The IGF delta relationship was minimally influenced by moderator variables such as thyroxine (T3, T4), and/or body mass index (BMI).

Conclusion. We conclude that age-adjusted IGF levels in healthy senior men co-vary significantly with SWS and the delta energy that characterizes it.

WITH advancing age there are declines in both sleep quality and the growth hormone (GH) system. Numerous cross-sectional studies have examined age effects on sleep. Studies of the subjective sleep complaints of the aged have consistently demonstrated that as many as 40% of elderly individuals sampled complain about sleep problems, including disturbed or "light" sleep, frequent awakenings, early morning awakenings, and undesired daytime sleepiness (1,2). The subjective complaints of poor sleep quality by the aged have been validated by repeatedly observed objective age changes in both the sleep EEG and in the amount and pattern of the various stages of sleep and wakefulness. The delta waves that characterize stage 3 and stage 4 sleep, the deepest stage of nonREM sleep as defined by arousal thresholds, are on average greatly attenuated in amplitude in the elderly (2,3). Older people spend on average more time in bed, and less time in deep (stage 3-4) sleep, although there is considerable variance, with some seniors showing minimal age change. Increased nighttime wakefulness and increased fragmentation of sleep by periods of wakefulness are common but not invariant, along with earlier bed times.

Growth hormone (GH) is an anterior pituitary peptide which exerts anabolic and growth-promoting effects at many tissue sites throughout the life span (4,5), particularly bone and muscle tissue. The anabolic effects of GH are mediated in part by GH's stimulation of insulin-like growth factor 1 (IGF-1) production in the liver and other tissues. IGF-1 in turn serves as part of a negative feedback loop regulating GH output. With aging there are declines in lean body mass (LBM) (6) and in the GH-IGF system (7–12). Parallel declines in IGF have also been observed (13,14). The hypothesis that age-related decreases in IGF and protein synthesis are due to an age decrease in GH secretion is supported by studies showing that exogenous GH administration restores plasma IGF to youthful levels in aged animals (15) and aged men (16,17). Similarly, GH restores protein synthesis in older animals (18) and LBM in older men (16). Thus, the age changes in the GH-IGF axis appear to be reversible, much as the estrogen drop during menopause is reversible.

Recent studies in young adults suggest a linkage between sleep and the GH-IGF axis. Sleep appears to be influenced by clinical extremes of GH status. Acromegaly is associated with an increased EEG power spectral energy during REM and delta sleep that normalizes when GH levels are normalized by effective treatment (19). Conversely, GH deficiency is associated with lower EEG delta energy during sleep and longer total sleep time (20). Sleep can be improved in response to acute GH administration (21) or stimulation of the GH-IGF axis using GHRH or other releasing factors: GHRH decreases awakenings and enhances slow wave sleep in young men (22–24) and in animals (25). Conversely, acute decreases in GH status in rats (due to a GH releasing factor antagonist) decrease slow wave amplitude and slow

wave sleep duration (26). This suggests that some of the variation in sleep quality in young adults might be related to status of their GH-IGF system. It is not known whether such a relationship exists in older adults.

With advancing age, GH-IGF values decline (8,13,14) as do measures of sleep quality (1). In this study we explore IGF and its relationship to sleep quality and the sleep EEG in health-screened older men.

METHODS

Subjects

Thirty healthy aged (50 to 75 yrs, $M = 64.3 \pm 6.6$ yrs) non-obese control men who participated in a larger study (MH33688) of the sleep EEG in normal aging, Alzheimer's disease, and major depression were the subjects of this study. All subjects were extensively screened for physical and psychological health by physical examination, clinical interview, and screening tests for depression (Hamilton Depression Score) and dementia (Folstein's Mini-Mental State Exam), and laboratory tests (27,28). All subjects reported normal sleep habits and were free from central nervous system active medications a minimum of 2 weeks prior to the study.

Procedures

Sleep recording and scoring. — Data reported here are from the second night of a two-night stay at the Clinical Research Center, University of Washington Medical Center. They received a standard hospital diet for the duration of the study. All subjects went to bed at their customary bedtime and slept until their customary risetime or until spontaneous awakening. Sleep recordings, including EEG, EOG, and EMG, were made following standard techniques (29). EEG electrodes were positioned for conventional sleep recordings at C3, C4, O1, O2 (international 10–20 system of measurement) and referred to contralateral mastoids. Data were obtained using a Grass Model 8–24 polygraph with filter settings of 0.1 and 70 Hz with the 60 Hz notch filter disengaged and digitized simultaneously at a 128 Hz real time sampling rate using a 12-bit digitizer installed in a 80386 microcomputer with a voltage range of ± 2.5 volts. All recordings were calibration corrected. Following data conditioning, the all-night data were computer scored for stages of sleep and wakefulness using power spectral analysis and an automated scoring algorithm (C STAGE) developed in our laboratory that corresponds well with conventional human ratings (30).

In addition, the power spectral analysis of the EEG during stages 2, 3, and 4 sleep was used to quantitate delta wave activity (.5 to 4 Hz) and other frequency bins during stages 2, 3, and 4 sleep. Because individual differences in cortex-to-skull anatomy can be quite large and can affect overall EEG amplitudes at all frequencies, we controlled for this unwanted variance by normalizing the EEG values. For this purpose, we divided a given subject's delta values by that same subject's normalization constant, defined as between a geometric mean of the ratios of that subject's power relative to a reference subject's power for frequency bins from 12 to 40 Hz during most quiescent, muscle-free sleep (31).

IGF-1 assay. — Plasma samples for IGF-1 assay were drawn the day preceding the all-night EEG. IGF levels were determined with a double antibody RIA, following extraction with acid-ethanol using Nichols reagents. The between-assay coefficients of variation at concentrations of 47, 150, and 600 ng/mL were 10.6%, 13.3%, and 10.0%, respectively. Because thyroid status can influence anabolic hormone systems, assays for T3 and T4 were also performed. T4 levels were determined by an antibody coated tube RIA method using commercial reagents (Diagnostics Products). The between-assay coefficients of variation at concentrations of 3.0, 7.7, and 14.5 μg/dl were 16.7%, 9.1%, and 6.9%, respectively. T3 determinations were performed by a chemiluminescent immunoassay utilizing Ciba-Corning reagents. The between-assay coefficients of variation at concentrations of 48, 164, and 283 ng/dL were 16.7%, 6.7%, and 8.9%, respectively.

Sleep variables included: average delta power per epoch of stages 2, 3, and 4 sleep; total delta power during stages 2, 3, and 4 sleep; stages 3 and 4 sleep (S34) as a percent of time in bed (% TIB); minutes of wake after sleep onset (WASO); wake (% TIB); total number of wakes lasting a minute or more (TAWI); REM (% TIB); and number of stage changes into wakefulness or stage 1 (STGCHG). Relationships with IGF were explored using multiple regression analyses with age as a covariate (i.e., forced first in all analyses). The influences of T3, T4, and BMI were also examined using stepwise forward multiple regression, again with age as forced covariate.

RESULTS

Table 1 shows the demographic and clinical characteristics of this healthy subject population. Subjects reported minimal depressive affect on the Hamilton Depression Rating Scale and normal mental status on Folstein's Mini-Mental State Exam. Table 2 shows the mean and standard deviation for IGF and EEG delta, sleep/wake stages, T3, T4, and BMI.

A strong positive relationship was found between IGF and various measures of delta sleep (Table 3). With age variance first removed, IGF explained 28% of the variance in average delta energy during stages 2, 3, and 4 sleep ($p < .003$) (partial correlation coefficient $r = .53$) (Figure 1). Significant and positive relationships were also observed for total delta energy ($r = .374$, $p < .04$) and S34 (% TIB) ($r = .424$, $p < .02$). In contrast, all non-delta measures of sleep quality were uncorrelated with IGF, including WASO, Wake %

Table 1. Demographic and Clinical Variables (Mean ± *SD*) for the 30 Healthy Male Subjects

	Mean	*SD*
Age	64.2	6.6
Years education	14.5	2.7
Hamilton Depression	3.4	2.9
Mini-Mental State Exam	28.0	2.1

Table 2. Mean and Standard Deviation of Delta Energy (μV^2 for .5 to 4 Hz), Sleep Quality, and IGF and Moderator Variable Values for the 30 Male Subjects

	Mean	*SD*
IGF ng/ml	156.9	37.0
Average delta/sleep epoch	14.6	3.3
Total delta/night	457.2	116.6
S34 (as % of TIB)	4.3	3.9
WASO (min)	104.7	59.1
Wake (as % of TIB)	26.6	12.6
TAWI	16.5	6.7
REM (as % of TIB)	13.7	5.4
STGCHG	39.2	11.2
T3 ng/dL	103.8	21.7
T4 μg/dL*	6.6	1.0
Body mass index	25.1	2.0

Notes. TIB = time in bed; WASO = waking after sleep onset; TAWI = total awakenings lasting 1 or more min; STGCHG = stage changes.

*T4 was not obtained for 4 subjects. For regressions including T4, the 4 missing values were replaced by the group mean of 6.62.

Table 3. Multiple Regressions (MRs) Showing Variance in Delta Sleep and Other Sleep Measures Explained (R^2) by IGF After Age Variance Is First Accounted for (r = Semi Partial Correlation Coefficient = $\sqrt{R^2}$)*

	R^2	r	p-value
Average delta energy (.5 to 4 Hz)	.281	.530	.003
Total delta energy	.140	.374	.04
S34 % TIB	.180	.424	.02
WASO	.067	.258	n.s.
Wake % TIB	.004	.063	n.s.
TAWI	.000	0	n.s.
REM % TIB	.019	.137	n.s.
STGCHG	.009	.094	n.s.

Notes. TIB = time in bed; WASO = waking after sleep onset; TAWI = total awakenings lasting 1 or more min; STGCHG = stage changes.

*For all MRs shown, age accounted for less than 4% (p = n.s.) of the variance.

TIB, TAWI, REM % TIB, and STGCHG (Table 3). In addition, we examined frequency bins in the sleep EEG other than delta (4 to 40 Hz). No significant correlations were found.

Multiple regressions were performed to determine the influence, if any, of thyroid hormones (T3,T4) and BMI in explaining variance in average delta energy. In all cases, these moderator variables failed to explain significant variance in delta energy (Table 4).

Discussion

The study's results indicate that plasma IGF levels correlated significantly and positively with measures of EEG delta activity during sleep, as well as delta sleep itself (stages 3 and 4) in healthy older men under normal (unstimulated) conditions. This IGF relationship is apparently specific to sleep-related EEG delta waves: no correlations were observed with other measures of sleep quality (wakefulness

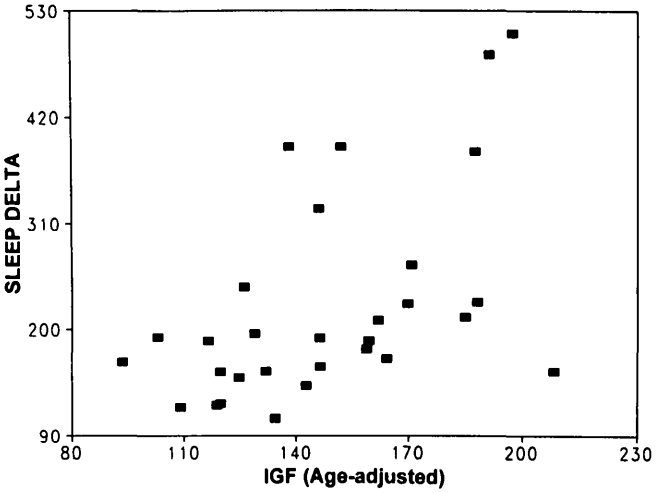

Figure 1. A scatterplot diagram of IGF (corrected for age) and average delta energy per epoch of slow wave sleep for 30 control males.

Table 4. Influence of Moderator Variables in Explaining Variance in Average Delta Energy*

	R^2 change	p-value
Age	.004	n.s.
IGF	.290	.005
T3	.040	n.s.
Body mass index BMI	–	n.s.
T4	–	n.s.

*All variables (IGF, BMI, T3 + T4) were allowed to enter a forward entry multiple regression where age was used as a covariate.

and REM measures), with EEG frequencies other than delta, or with moderator variables (BMI, T3, T4). The correlation is based on stable measures; repeated measures for both IGF1 and delta sleep are stable over time in healthy seniors studied in our laboratory (32,33).

Together with other clinical studies reviewed above, these results suggest a linkage between a peripheral index of anabolic status (IGF) and a central nervous system function (sleep). Current understanding of the neurobiology of GH-IGF is sufficiently advanced that a variety of mechanisms could be postulated: The IGF peptide, the Type I IGF receptor, mRNA, and IGF binding proteins have been widely localized in the brain (34,35). Studies based on biosynthetic labeling or on local gene expression suggest that IGF may be both synthesized in the brain and taken up from the peripheral circulation (36). Type I IGF receptors are especially prevalent in the hypothalamus, the choroid plexus, and the circumventricular organs (CVOs); (34,36). IGF also binds with high affinity to the cerebral cortex and the hippocampus. Peripheral GH and IGF could act directly on the brain via areas lacking in blood-brain barrier (the CVOs) (37) or via transport through the choroid plexus and into CSF-bathed tissues containing receptors (38). The median eminence, with its high density of Type I IGF receptors (39), lacks a blood-brain barrier and is bathed by CSF. IGF has been implicated in CNS functions, including

control of GH release (40) and regulation of satiety states (41–43).

GHRH and its receptors are also localized in a variety of brain sites (44), including the hypothalamus, where its role may include that of neurotransmitter/neuromodulator in addition to controlling GH release; mRNA for the GH receptor has been found in the brain (45), as has GH-like material (46), and there is evidence for retrograde transport of pituitary-synthesized peptides into the hypothalamus.

In short, the brain contains all of the elements of a functional and potentially important signaling system based on GHRH-GH-IGF. In addition, the recent studies described above provide possible anatomical mechanisms for some sort of link between circulating GH-IGF and central GHRH-GH-IGF. The presence of such a link is further supported by the finding that IGF receptors in brain tissue can respond to variations in plasma IGF levels (39). The biggest question concerns the neurobiological role of these peptides. In addition to an important role in the development, maintenance, and metabolism of the CNS (47), they may also serve as neuromodulators important for some brain functions. Steiger et al. (22) raise the possibility that hypothalamic GHRH may stimulate both GH release and delta sleep; they suggested that delta sleep increases following GHRH may outlast and/or exceed the GH response to GHRH. Whatever the mechanism proves to be, the preliminary data presented here suggest that delta sleep covaries with the unstimulated status of the GH-IGF system in older adults.

In conclusion, the relationship between naturally occurring IGF and sleep quality observed here suggests that enhanced GH-IGF status may improve delta sleep in older men and/or vice versa. Future research may elucidate these possibilities.

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