

THE TEMPORAL RELATION BETWEEN HGH RELEASE AND
SLEEP STAGE CHANGES AT NOCTURNAL SLEEP ONSET IN MAN

Michael A. Pawel, Jon F. Sassin, Elliot D. Weitzman

Montefiore Hospital and Medical Center, The Albert Einstein College of Medicine,
Bronx, New York

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Summary

The temporal pattern of growth hormone release at sleep onset was studied in six adult human subjects by frequent blood sampling combined with polygraphic sleep recording. HGH release was associated with sleep onset but not with the transition from waking to sleep. Delta activity consistently preceded the first elevation of plasma HGH.

A marked rise in plasma human growth hormone (HGH) regularly follows the onset of nocturnal sleep in adults (1-4). This rise can be diminished or delayed by experimental reduction of polygraphically defined sleep stages 3 and 4 (5-7), but it apparently is not associated with changes in the known metabolic substrates of HGH, such as plasma glucose concentration (8). In previous studies, plasma was sampled at 20 to 30 minute intervals and polygraphic records were scored in 30 second or 1 minute epochs. Thus, plasma sampling frequency was the limiting factor in analyzing the temporal relationship between EEG sleep stages and the onset and pattern of hormone concentration changes in the blood. In an attempt to define this relationship more precisely, we sampled plasma for HGH at 4 minute intervals during and for about 90 minutes after the transition period from waking to sleep, and scored polygraphic records in 10 second as well as 30 second epochs.

Methods

The subjects studied were four men and three women between ages 23 and 31 years. They were in good health, were not using drugs, and habitually slept at night. Each subject spent one adaptation night followed by two experimental nights in the sleep laboratory. Standard polygraphic electrodes for

electroencephalography (EEG), electromyography (EMG), and electrooculography (EOG) (7) and an indwelling venous catheter on experimental nights were placed at 6 PM (9). Subjects were then fasted and remained at bedrest for the subsequent 12 hours. Lights were turned off at 10 PM and subjects instructed to go to sleep. Lights were turned on at 6 AM and the experimental session terminated.

At 20 minute intervals until lights out, heparinized blood samples of 4 cc each were drawn from an adjoining room through a 5-foot polyethylene catheter kept patent with heparinized saline (9). Polygraphic records were monitored as they were obtained, and from the onset of stage 1 sleep (7) blood samples were drawn every 4 minutes throughout the first short-term sleep cycle. Sampling intervals were then increased to 10 minutes and then 20 minutes, spaced through the rest of the night so that the total number of samples did not exceed 60 per session. Plasma was separated by centrifugation and frozen immediately.

HGH concentration was determined in duplicate on each sample by radioimmunoassay using charcoal-dextran separation of bound from free hormone (10) (HGH standard: Wilhelmi HS 1216 C). Plasma concentrations of HGH above one nanogram per milliliter were detectable by this method. Polygraphic records of experimental nights were scored by applying the standard criteria of the sleep manual (7) to 30 second epochs and then independently to 10 second epochs. All scoring was done by one of the authors (MAP) with independent scoring by another (JFS) showing greater than 90% agreement. Sleep data from the adaptation nights was not analyzed. There were no consistent differences between the sleep profiles of the two experimental nights.

Results

Table 1 summarizes the data from six subjects on 10 nights. The pattern in the three women subjects was somewhat irregular. One failed to release HGH during the entire period studied and is, therefore, not shown in Table 1. The two others (subjects 2 and 4), released HGH prior to sleep onset, obscuring the initial phase of the sleep onset rise on the first nights when blood was

drawn. On the second nights, these two subjects demonstrated markedly shorter latencies between sleep onset and HGH release than the other subjects.

TABLE 1

Onset of HGH Release

Subject	Sex	Expt'l Night	Time (min.*) from Sleep Onset to:		
			First 10 sec. Epoch Stage 3	First Elevated Blood Sample	First 30 sec. Epoch Stage 3
1	M	1	9	9	11.5
		2	6.5	11	11.5
2	F	2	2.5	8.5	9.5
3	M	1	15	18.5	19
		2	9	26.5	11
4	F	2	1.5	2	8
5	M	1	9.5	70	11.5
		2	5	39	10.5
6	M	1	29	44	31
		2	17.5	31	21.5
Mean			9.5	26	14.5

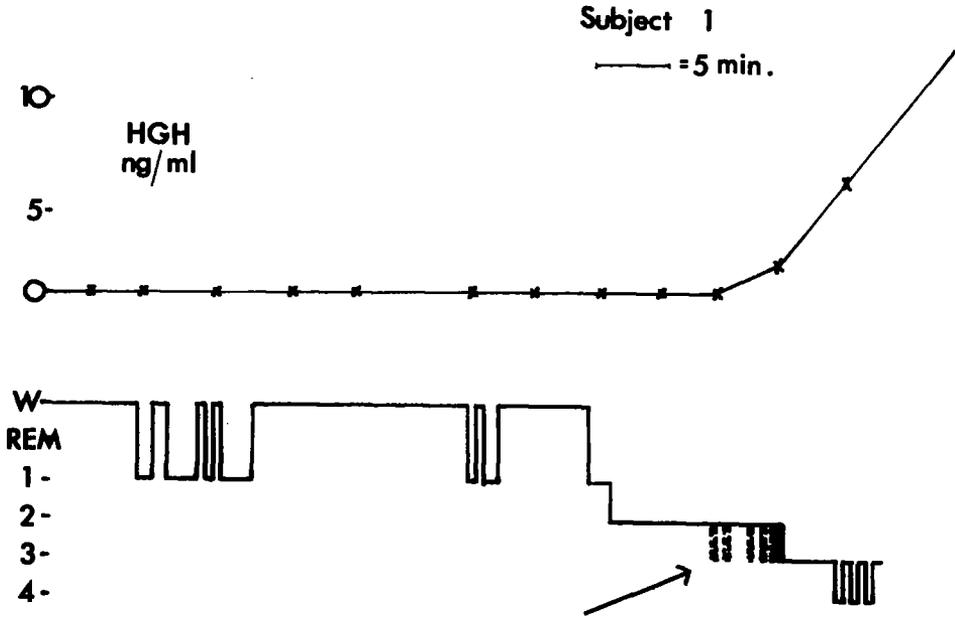
* to the nearest half minute.

Delta activity (1-3 Hz) consistently occurred before the first sample showing increased HGH concentration was drawn. On four nights, slow wave development was insufficient to justify scoring a 30 second epoch as Stage 3 until after the initial HGH rise. Consideration of 10 second epochs, however, resulted in scorable Stage 3 which preceded the first HGH elevation in every case but one where the events were noted simultaneously. On nine of the ten nights, at least one and as many as 13 blood samples were drawn in the interval between sleep onset and the first sample showing HGH elevation, indicating that the sampling rate was sufficiently rapid to avoid more than a fractional overestimation of this interval.

Figure 1 is a combined plot of plasma HGH concentration and sleep stage illustrating the sequence of the events studied around sleep onset on a

typical night from one subject (#1) who was representative of all the men studied.

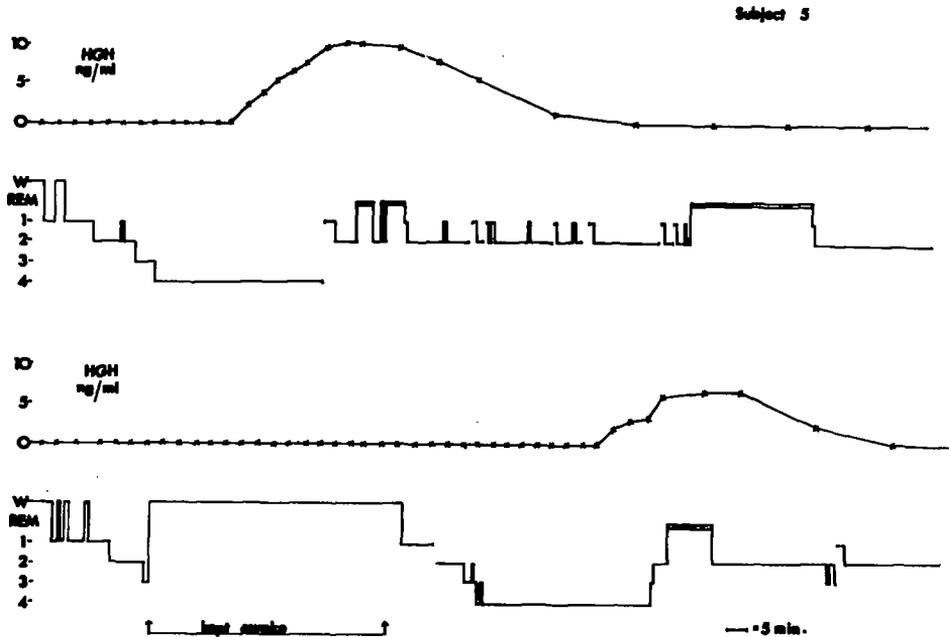
FIG. 1



Sleep stages are based on scoring the record in 30 second epochs. The broken line histogram (arrow) indicates the first occurrence of Stage 3 when the record was scored in 10 second epochs. The subject was awake in the dark for over an hour before the period shown. This prolonged period of drowsiness, characterized by a mixture of wakefulness and brief periods of Stage 1, was not associated with a rise in plasma HGH. When Stage 2 was well established and slow wave activity had begun, the first increase in HGH plasma concentration was noted. In this case, the first sample showing elevated HGH was drawn half a minute before the earliest 30 second epoch that could be scored as Stage 3. Ten-second epochs of Stage 3, however, could be scored during the 5 minutes preceding this first elevated sample.

Figure 2 shows the results of interrupting sleep at the occurrence of the first slow wave activity, a procedure carried out with only this subject (#5).

FIG. 2



On the control night (upper graph) the subject began releasing HGH about one half hour after onset of Stage 3. On the experimental night (lower graph) sleep was interrupted for one hour (between arrows) at the onset of Stage 3 and then allowed to proceed undisturbed. HGH release did not occur until about one-half of uninterrupted slow wave sleep had occurred. The release pattern after interruption was similar to that on the control night. HGH concentrations were not available at the time this manipulation was performed, and it remains undetermined whether the brief occurrence of Stage 3 might herald onset of HGH release in subjects who regularly demonstrated a shorter latency between the two phenomena.

Although scoring sleep records in 10 second epochs demonstrated a

consistently earlier onset of slow wave sleep in the first sleep cycle, the mean overall percentages of the different sleep stages changed less than two percent when compared with scoring in 30 second epochs, differences involving only 10 minutes of each night.

Comments:

A release of HGH is associated with the change from the waking state to sleep. The results of this study indicate that the transitional events between waking and definitive sleep (rest, Stage 1, and brief periods of Stage 2) are not sufficient to elicit this release. The events leading to release of HGH occur subsequent to this transition, and appear to coincide with the development of definitive sleep, characterized by slow synchronous electrocortical activity. This temporal sequence, however, does not necessarily imply a cause and effect relationship, since both HGH release and slow wave activity are known to occur independently of each other. For example, arginine infusion, hypoglycemia, venipuncture, and non-specific stress are known to precipitate HGH release (11), although they are unrelated to sleep, while slow wave sleep during the later night has been recorded without accompanying HGH release (3). Nevertheless the consistent correlative temporal pattern described here does suggest that an underlying mechanism which remains unelucidated, precipitates both onset of deep sleep and release of HGH.

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