Methscopolamine Inhibition of Sleep-Related Growth Hormone Secretion

EVIDENCE FOR A CHOLINERGIC SECRETORY MECHANISM

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ABSTRACT We have examined the effects of cholinergic blockade with 0.5 mg methscopolamine bromide, intramuscularly, on sleep-related and insulin-induced growth hormone (GH) secretion. 17 normal young men were studied; 8 had sleep studies, and 12 (including 3 who also had sleep studies) had insulin tolerance tests (ITT) with 0.1 U/kg of regular insulin. After an adjustment night in the sleep laboratory, saline control night and methscopolamine night studies were done in random sequence; study procedures included electroencephalographic, electromyographic, and electrooculographic recordings, and blood sampling every 20 min for hormone radioimmunoassays. Prolactin levels were also measured during sleep. For methscopolamine night studies, the mean overall control GH level of 2.89±0.44 ng/ml and the mean peak control GH level of 11.09±3.11 ng/ml were dramatically reduced to 0.75±0.01 and 1.04±0.25 ng/ml, respectively ($P < 0.0001$ and <0.001). Despite virtual absence of GH secretion during the night in every study subject, no measured sleep characteristic was affected by methscopolamine, including total slow-wave sleep (12.1±2.6% control vs. 10.3 ±2.5% drug, $P > 0.2$). Sleep prolactin levels were not changed by methscopolamine. In contrast to the abolition of sleep-related GH secretion, administration of methscopolamine had only a marginal effect on the GH response to insulin hypoglycemia. None of nine time points differed significantly, as was also the case with peak levels, mean increments, and areas under the curves ($P > 0.2$). Analysis of variance did, however, indicate that the lower GH concentrations achieved during ITT after methscopolamine (average 31.7% below control) were significantly different than control concentrations. We conclude that the burst of GH secretion which normally occurs after sleep onset is primed by a cholinergic mechanism which does not influence slow-wave sleep. Cholinergic mechanisms do not appear to play an important role in sleep-related prolactin secretion. The contrast between the complete suppression of sleep-related GH release and the relatively small inhibitory effect on ITT-induced GH secretion suggests that the neurotransmitter mechanisms, and presumably the pathways, which subserve sleep-related GH secretion in man may be different from those which mediate the GH response to pharmacologic stimuli such as insulin.

INTRODUCTION

The secretory patterns of growth hormone (GH)[1] and of prolactin (PRL) are related to normal sleep. GH secretion is enhanced during the 90–120 min immediately following sleep onset in temporal association with periods of slow-wave sleep (1–3). As much as

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[1] *Abbreviations used in this paper*: ANOVA, analysis of variance; GH, growth hormone; ITT, insulin tolerance test; PRL, prolactin; REM, rapid-eye-movement.

70–90% of the total 24-h production of GH in adults may occur during these 2 h. Elevated PRL levels during sleep do not occur in a well-defined major secretory episode as is the case for GH; rather, substantial episodic irregularity prevails throughout the night, with highest levels occurring during the latter half of sleep (4, 5). It has been reported (6), but not confirmed (7), that nocturnal elevations in PRL levels are temporally related to the termination of periods of rapid-eye-movement (REM) sleep. For both hormones, a number of control experiments have indicated that the enhanced nocturnal hormone secretion is sleep-entrained, and not related to an intrinsic circadian rhythm or due to other sleep-associated parameters. These controls have included sleep deprivation, and studies of interrupted or shifted sleep (1, 4, 5, 8).

A number of attempts have been made to modify sleep-related GH secretion. No detectable effect occurred with diphenylhydantoin, pentobarbital (1), chlorpromazine (1), hyperglycemia (9–12), phentolamine (11), or propranolol (11). However, a variety of factors has been found to be capable of suppressing sleep-related GH release, some without observable effect on slow-wave sleep (1, 13–21). These include: imipramine (1), medroxyprogesterone acetate (13), clomiphene (14), cyproheptadine (15), somatostatin (16), free fatty acids (17), relative obesity (18, 19), advanced age with acromegaly (20), the dwarfism associated with emotional deprivation (21), and chronic alcoholism (22). In most of these instances, no effect on slow-wave sleep was noted, and in one study, the amount of slow-wave sleep increased on nights when sleep-related GH secretion decreased (15). Further, inhibition of slow-wave sleep with flurazepam was not accompanied by any change in sleep-related GH secretion (23). Thus, the association of enhanced GH secretion at sleep onset with slow-wave sleep appears neither causative nor obligate. The same conclusion was reached by Martin in a recent review (24).

Identification of factors capable of influencing central neurotransmission which can also modulate sleep-related GH secretion may help to establish the neural pathways and mechanisms which subserve physiologic GH release. Among the approaches to the study of neuropharmacologic modification is the use of receptor blocking agents. In previous work, we have demonstrated the moderate stimulatory effect on sleep-related GH secretion of the serotonin receptor-blocking drug, methysergide (7). Sleep-related PRL secretion was profoundly suppressed by methysergide. In an ongoing study of the effects of neurotransmitter-modulating agents on sleep-related pituitary hormone secretion, we report in this paper the effect of cholinergic receptor blockade with methscopolamine bromide on sleep electroencephalogram (EEG) parameters, and serum GH and PRL levels. Because of our previous demonstration of antipodal effects of methysergide on sleep-related and insulin-provoked GH release (7), and therefore the probability that different stimuli to GH release involve different neuropharmacologic pathways, we have also assessed the effect of this agent on insulin-induced GH secretion.

METHODS

Subjects for the study on sleep-related secretion were eight normal paid volunteers between the ages of 19–30 yr. Insulin-provocative testing was also performed on 12 similar subjects, including 3 who had participated in the sleep study. The height/weight ratio of all subjects was 2.36±0.08 cm/kg (19). All subjects had the following normal studies: medical history, physical examination, complete blood count, blood chemistry profile and chest X ray. Written informed consent was obtained after a detailed verbal and written explanation of the study.

Both the sleep and insulin studies were performed with a double-blind crossover design; the drug and placebo were administered in random sequence. For the sleep study, an acclimatization night without blood sampling preceded the two study nights; subjects reported to the laboratory at 8:00 p.m., at which time a catheter was inserted into a forearm vein. At 10:00 p.m., either 0.5 mg methscopolamine bromide or 0.5 cm^3 normal saline was administered intramuscularly, and at 10:30 p.m., the subject went to bed. A unipolar EEG, horizontal electrooculogram, and electromyogram were recorded from 10:30 p.m. until 7:30 a.m. Recordings were performed on a model 7 polygraph (Grass Instrument Co., Quincy, Mass.) with a paper speed of 10 mm/s, calibrated for 50 μV to produce a 7.5-mm deflection. Recordings were read blindly by a single investigator using sleep-stage criteria of Rechtschaffen and Kales (25). During the night, 5-cm^3 samples of blood were taken every 20 min from the venous catheter, for hormone analysis. The catheter was kept open by slow infusion of 0.45% saline containing 3,000 U of heparin/liter. The total amount infused was up to 500 ml of this solution.

For the insulin tolerance tests, fasting subjects reported to the laboratory at 8:00 a.m., at which time a scalp vein needle was inserted into a forearm vein, and a slow infusion of 0.45% saline was started. At 8:30 a.m. the subjects received 0.5 mg methscopolamine or 0.5 cm^3 saline intramuscularly, and at 9:00 a.m., 0.1 U/kg of regular insulin was administered intravenously. 5-cm^3 blood samples were drawn for glucose and hormone measurement every 15 min for 2 h. All specimens for GH and PRL assay were allowed to clot, the serum was promptly separated and stored at −18°C.

Determinations of GH and PRL were performed by radioimmunoassay (26, 27). The antisera, standards and tracer, and current details of the GH method have been recently described (28). The usual sensitivities of the assays were 0.5 ng/ml of serum for GH and 1.5 ng/ml for PRL. Blood glucose determinations were done using a glucose oxidase technique. Hormonal data during sleep were processed by an analysis of variance (ANOVA) derived from the Statistical Analysis System computer package (29). For the purposes of this analysis, the data were divided into three time periods, hours 1 and 2, hours 3 and 4, and hours 5–8 after the start of sleep. The data were subjected to a logarithmic_{10} transformation for normalization (30), and partial sums of squares were employed because of the unbalanced, nonorthogonal design. This analysis allowed separate examination of the contributions of the total variance of differences between subjects, the effects of time period, sleep stages, and drug treatment, and the interactions between treatment and time period and between treatment and sleep stage (Tables III and V). For the purpose of statistical analysis, all hormonal determinations which were undetectable were assigned a value equal to the detection limit in the particular assay in which they were included. All samples from any one subject were included in the same assay.

As usual, the GH responses during ITT exhibited great variability among subjects; a wide range of values was observed for the magnitude, time of onset of rise, and time of peak increment. Therefore, these data were analyzed in a variety of ways, both before and after $\log_{10}$ transformation for each method of analysis. Mean GH levels at each time point were compared by paired and nonpaired t test. Peak GH levels, maximum GH increments over base line, and areas under the GH curves were subjected to paired t test. In addition, these data comparisons were also evaluated by a two-way ANOVA in the determination of a possible drug effect (7). A table was constructed by subtracting the GH value at each time during the drug ITT from the corresponding GH value for the same time and from the same subject during the placebo ITT. In this table of differences, the 12 columns represented the 12 subjects and the 9 rows represented the sampling times during ITT (0,15,30,45,60,75,90,105, and 120 min). In addition, to avoiding the problem of nonindependence of multiple time points, this approach also permits the determination of whether or not the two GH curves (Fig. 2) deviate from parallelism with each other. Such a deviation is indicated if the effect of time is significant in the ANOVA, since the difference between the two curves is the data base. The effect of drug treatment is determined by posing the question whether or not the overall mean of these data is significantly different from zero. If not, the treatment is indicated not to have affected the GH response to ITT. For the purposes of statistical analyses, all values of GH and PRL which were below the limit of detectability were recorded as being equal to that value. The results of all statistical analyses were similar whether original data or $\log_{10}$ transformed data were used.

RESULTS

Sleep. Analysis of the sleep parameters is presented in Table I. Methscopolamine did not affect the total sleep time, percentage of any individual sleep stage, or any other measured sleep parameter. In view of the interest in the relation of GH secretion to slow-wave sleep, it should be noted that total slow-wave sleep (stages 3 and 4 combined) was also unchanged.

Growth hormone. Sleep-related GH levels are shown in Fig. 1. The mean±SE GH values for each sleep stage and time period on placebo and methscopolamine nights are given in Table II, and the results of the ANOVA for GH levels are presented in Table III. It is evident that administration of methscopolamine was associated with profound suppression of GH secretion. The overall mean GH level of 2.89±0.44 ng/ml and the mean peak of 11.09 ±3.11 ng/ml during the placebo night were reduced by methscopolamine to 0.75±0.01 and 1.04±0.25 ng/ml, respectively ($P < 0.0001$ and < 0.001). In fact, <3% of samples obtained on the methscopolamine nights contained detectable GH levels, and the highest value recorded on all drug nights was 2.6 ng/ml. This virtual absence of GH secretion after the administration of methscopolamine contrasts with the normal GH pattern on placebo nights, the highest values occurring in a well-defined secretory episode during the first 2 h of sleep. ANOVA revealed both time period alone and time-drug treatment interaction to be highly significant variables, reflecting the normal occurrence of hormone secretion in early sleep ($P < 0.0001$ for both parameters, Table III). A significant treatment-sleep stage interaction was also detected ($P < 0.02$), reflecting the dominant drug effect on GH secretion during stage 4

TABLE I
*Sleep Parameters in Eight Normal Subjects Given 0.5 mg Methscopolamine**

	Methscopolamine	Placebo	Significance level‡
Total sleep time, *min*	390.6±13.5	353.0±27.3	NS
Stage 1, %	2.5±1.2	3.3±1.4	NS
Stage 2, %	64.9±3.0	61.0±2.3	NS
Stage 3, %	7.2±1.9	8.3±1.6	NS
Stage 4, %	3.1±1.0	3.8±1.8	NS
Total slow-wave sleep, %	10.3±2.5	12.1±2.6	NS
Stage REM, %	23.3±1.6	22.2±2.3	NS
REM latency, *min*	122.2±13.6	107.6±17.8	NS
REM density (0–8)	1.6±0.2	1.7±0.1	NS
Intermittent waking, *min*	20.4±10.8	31.2±14.6	NS

* Values presented as mean±SE.
‡ Two-tailed paired t test with df = 7. Arcsine transformation was performed on data given as percentages.

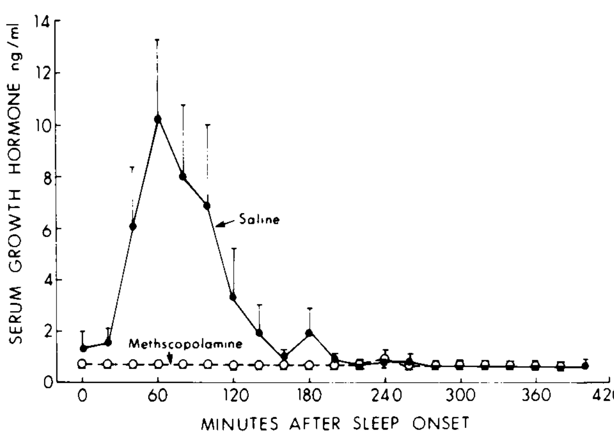

FIGURE 1 GH concentrations during the night are shown (mean±SE). All data are synchronized according to sleep onset, electroencephalographically defined. ●, Control nights; ○, methscopolamine treatment nights.

TABLE II
Effect of Methscopolamine on Sleep-Related GH Secretion

	Hours 1 and 2		Hours 3 and 4		Hours 5 to 8		Total (sleep stages)
	Drug	Placebo	Drug	Placebo	Drug	Placebo	
Intermittent waking	0.70±0.00 (1)	6.22±4.78 (6)	0.70±0.00 (1)	1.20±0.63 (3)	0.64±0.11 (5)	0.50±0.00 (3)	2.47±1.47 (19)
Stage 1	0.50±0.00 (1)	0.50±0.00 (1)	— (0)	— (0)	0.50±0.00 (1)	0.50±0.00 (1)	0.50±0.00 (4)
Stage 2	0.85±0.16 (29)	7.04±1.73 (21)	0.78±0.09 (25)	2.53±0.62 (23)	0.70±0.04 (28)	0.74±0.05 (35)	1.84±0.29 (161)
Stage 3	0.81±0.12 (7)	3.94±2.33 (5)	— (0)	3.30±2.45 (5)	— (0)	0.50±0.00 (1)	2.36±0.87 (18)
Stage 4	0.83±0.21 (3)	11.08±4.11 (4)	0.70±0.00 (2)	2.90±0.00 (1)	0.70±0.00 (1)	— (0)	4.71±2.03 (11)
REM	0.80±0.08 (4)	0.70±0.00 (1)	0.70±0.09 (7)	0.90±0.13 (7)	0.68±0.05 (18)	0.75±0.07 (13)	0.74±0.03 (50)
Total (treatment)	0.83±0.10 (45)	6.59±1.27 (38)	0.76±0.07 (35)	2.24±0.46 (39)	0.68±0.03 (53)	0.72±0.04 (53)	
Total (time)	3.47±0.66 (83)		1.54±0.26 (74)		0.70±0.02 (106)		

Values represent mean±SEM in nanograms per milliliter. Parentheses refer to number of samples which were obtained during indicated sleep stage and time period.

sleep (>10-fold reduction, Table II). Due to the similarity of all GH values during methscopolamine study nights, the relation of individual sleep stages to GH levels did not reach statistical significance in the entire data set ($P < 0.08$, Table III), but a highly significant relationship obtained when only the placebo night GH data were considered.

The GH response to insulin-induced hypoglycemia after injection of saline or methscopolamine is shown in Fig. 2. The magnitude and duration of the hypoglycemia were virtually identical in both circumstances. The GH response during the control insulin tolerance test reached a peak of 39.4±9.5 ng/ml at 75 min; the mean of the individual peaks, 43.9±10.2 ng/ml, represented a mean maximum increment over basal GH levels of 42.9 ng/ml. After methscopolamine, a similar GH peak of

TABLE III
ANOVA: Sleep-Related GH Secretion

Source	df	Partial sum of squares	F	P
Subjects	7	4.0952	14.7416	<0.0001
Drug treatment	1	1.0392	26.1875	<0.0001
Time period	2	2.2073	27.8097	<0.0001
Treatment-time period interaction	2	1.9010	23.9506	<0.0001
Sleep stage	5	0.3950	1.9908	<0.0799
Treatment-sleep stage interaction	5	0.5552	2.7983	<0.0176
Error	238	9.4451		
Total	260	23.5225		

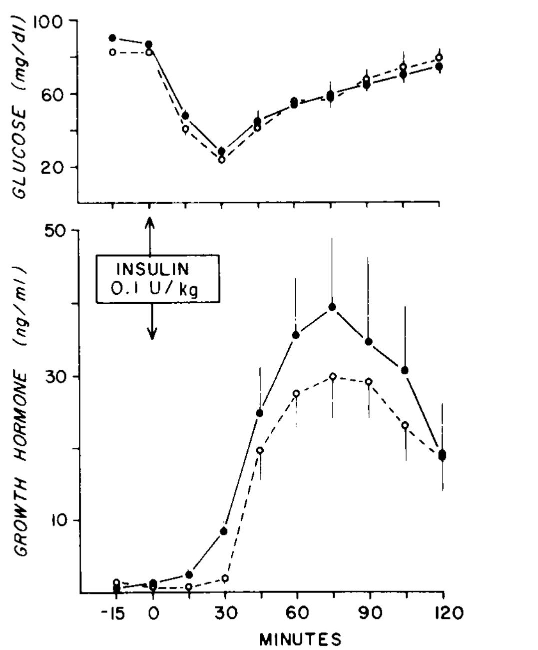

FIGURE 2 Concentrations of GH and glucose during ITT are shown. ●, Control studies; ○, methscopolamine studies.

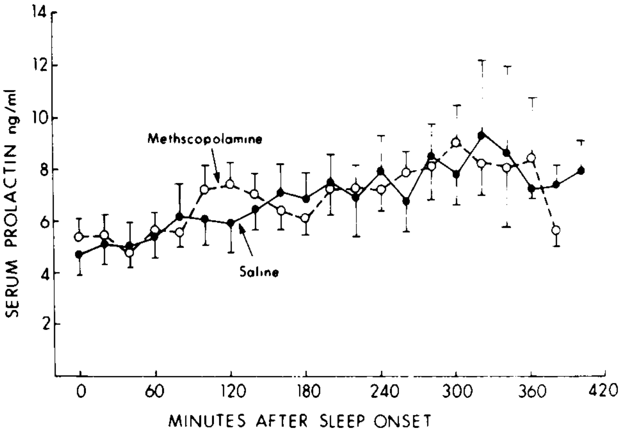

FIGURE 3 PRL concentrations during the night are shown (mean±SE). Data are synchronized according to sleep onset, electroencephalographically defined. ●, Control nights; ○, methscopolamine treatment nights.

30.0±6.4 ng/ml ($P > 0.2$) also occurred at 75 min; the mean of the peaks, 35.6±6.1 ng/ml, and the mean maximum increment, 34.2 ng/ml, were also not significantly different from the control values ($P > 0.2$ for both). Similarly, the areas under the GH curves were not significantly different. However, the rise in GH during the control ITT occurred earlier than that during the methscopolamine ITT; the mean control GH at 30 min, 8.13±2.29 ng/ml, was higher than the corresponding value during the methscopolamine ITT (1.84±0.62 ng/ml), but this difference fell short of statistical significance ($P > 0.05$). Comparisons of the other time points did not reveal any differences. Despite the general lack of statistical significance by the above tests, it should be noted that all mean GH values after insulin are a bit lower after methscopolamine than after saline. In keeping with this fact, the two-way ANOVA did show a significant difference ($F = 9.71$, $P < 0.01$) between the two GH curves attributable to a drug rather than a time effect. The average reduction as a percentage of area under the curves was only 31.6%, however.

PRL. Sleep-related PRL secretion is pictured in Fig. 3. The PRL concentrations during the study nights are presented in Table IV, and the results of the ANOVA are found in Table V. As in the case of GH, there were great differences between individuals. Neither sleep stages, methscopolamine treatment, nor interaction effects had a significant influence on nocturnal PRL levels. The concentrations of PRL were in fact nearly identical through most of the observation period (Fig. 3). However, PRL levels were significantly related to the time of night, with values increasing toward morning ($P < 0.0001$, Table V).

TABLE IV
Effect of Methscopolamine on Sleep-Related PRL Secretion

	Hours 1 and 2		Hours 3 and 4		Hours 5 to 8		Total (sleep stages)
	Drug	Placebo	Drug	Placebo	Drug	Placebo	
Intermittent waking	4.80±0.00 (1)	6.00±0.99 (6)	9.90±0.00 (1)	4.90±0.00 (3)	8.70±1.83 (5)	8.83±2.60 (3)	7.13±0.72 (19)
Stage 1	5.70±0.00 (1)	5.20±0.00 (1)	— (0)	— (0)	11.20±0.00 (1)	5.40±0.00 (1)	6.88±1.67 (4)
Stage 2	6.03±0.41 (29)	5.39±0.55 (21)	6.46±0.36 (25)	6.36±0.60 (23)	7.52±0.50 (27)	7.93±0.62 (35)	6.73±0.22 (160)
Stage 3	4.98±0.90 (7)	5.28±1.68 (5)	— (0)	8.80±1.22 (5)	— (0)	7.20±0.00 (1)	6.25±0.71 (18)
Stage 4	6.93±3.30 (3)	3.95±0.38 (4)	5.30±0.00 (2)	9.20±0.00 (1)	12.80±0.00 (1)	— (0)	6.29±1.10 (11)
REM	6.90±0.99 (4)	2.20±0.00 (1)	7.16±0.87 (7)	5.81±1.23 (7)	7.02±0.66 (18)	6.61±0.39 (13)	6.66±0.33 (50)
Total (treatment)	4.97±0.34 (45)	5.23±0.40 (38)	6.63±0.32 (35)	6.54±0.45 (39)	7.63±0.39 (52)	7.59±0.44 (53)	
Total (time)	5.63±0.26 (83)		6.58±0.28 (74)		7.61±0.29 (105)		

Values represent mean±SEM in nanograms per milliliter. Parentheses refer to number of samples which were obtained during indicated sleep stage and time period.

Table V
ANOVA: Sleep-Related PRL Secretion

Source	df	Partial sum of squares	F	P
Subjects	7	2.9179	29.9325	<0.0001
Drug treatment	1	0.0441	3.1653	<0.0765
Time period	2	0.4638	16.6517	<0.0001
Treatment-time period interaction	2	0.0171	0.6153	<0.5464
Sleep stage	5	0.0769	1.1048	<0.3584
Treatment-sleep stage interaction	5	0.0929	1.3345	<0.2493
Error	238	3.3144		
Total	260	7.1934		

DISCUSSION

We have found that nocturnal administration of a single 0.5-mg dose of methscopolamine abolished sleep-related GH secretion. This was a specific effect; sleep-related secretion of PRL was unaltered, and GH secretion provoked by insulin hypoglycemia was only marginally affected.

The effect of methscopolamine on insulin-induced GH secretion was not significant by any of the methods of statistical assessment employed save one, the ANOVA. This was true whether the raw data or the $\log_{10}$ transformed data were used. The difference in the magnitude of methscopolamine action in the two GH secretory situations is so great that a qualitative difference in the mechanisms of action must be one of the possibilities entertained to explain the discrepancy. We have previously reported an even more marked dissociation of pharmacologic effects on sleep-related and insulin-induced GH secretion (7). In that case, methysergide, a serotonin receptor blocker, was found to produce increased sleep-related, but decreased insulin-induced secretion. Thus, there is precedent for the belief that the mechanisms, and probably the neural pathways, involved in the control of physiologic sleep-related GH secretion may well be different from those which are involved in GH control in response to insulin or other pharmacologic provocation. However, since the ANOVA did indicate a significant suppressive effect during the ITT, it is possible in the case of methscopolamine that the same pathway is differentially sensitive to methscopolamine under the two different study conditions, one during overnight sleep, and the other in the morning.

Table VI
ANOVA: Insulin-Induced GH Secretion

Source	df	Sum of squares	F	P
Subjects	11	28.9467	4.3417	<0.001
Time	8	3.5456	0.7312	NS
Drug treatment	1	5.8834	9.7069	<0.01
Error	88	53.3337		
Total	108	91.7094		

Two-way analysis of variance with replicates. Data were subjected to $\log_{10}$ transformation before analysis. The data base is the difference, at each time, for each subject, between the GH values during the control test and those during the methscopolamine test.

We presume that the profound suppression of sleep-related GH levels observed in this study after administration of methscopolamine bromide is related to the anticholinergic properties of this agent. The dose employed was relatively small, and the pharmacologic specificity of action of the belladonna alkaloids is quite good as long as very large doses are not used (31). Inasmuch as quaternary ammonium derivatives like methscopolamine bromide do not readily cross the blood-brain barrier (31–35), the site of drug action in the studies reported here may well be in the median eminence or its immediate environs, one of the few areas in the central nervous system with an incomplete blood-brain barrier, or possibly in the pituitary itself. However, such putative sites of action cannot be in a main final common neural pathway, since the drug was relatively impotent in blocking the GH response to insulin hypoglycemia.

There are few data bearing on the possible role of the cholinergic system in GH regulation in man. Salvadorini et al. (36) have described increased daytime GH secretion in response to intravenous administration of cytidine diphosphate choline. These data, as well as those we have obtained, suggest that the cholinergic system plays a facilitatory role in GH secretion, assuming bioavailability of choline from this agent to serve as an acetylcholine precursor. If further data continue to support the interpretation that cholinergic influences may stimulate GH secretion, than an explanation for previous apparently discrepant findings may emerge. We have reported increased GH levels during sleep after methysergide, a serotonin blocker of high pharmacologic specificity (7). In contrast, Chihara et al. (15) have reported suppression of GH levels during sleep after cyproheptadine, a drug which has serotonin-, histamine-, acetylcholine-, and dopamine-blocking properties (37, 38). Cyproheptadine is in fact a rather potent anticholinergic, and its ability to suppress GH levels during sleep may be related to its anticholinergic properties. In this regard, it also seems plausible that the suppressive effects of imipramine on sleep-related GH secretion observed by Takahashi et al. a decade ago (1) were caused by the substantial anticholinergic effects of this drug rather than by its effects on amine re-uptake. There is no available information at present on the effects of anticholinergic drugs on daytime GH responses to secretagogues other than insulin.

Despite profound suppression of sleep-related GH secretion, methscopolamine had no effect on sleep in the present study (Table I). Failure of this drug to affect sleep has been previously reported (39), and is presumably due, at least in part, to its poor penetrance of the blood-brain barrier (31–35). These considerations suggest, as noted above, that the effects of methscopolamine on sleep-related GH secretion are probably exerted at the level of the hypothalamus or the pituitary. Failure to block the GH response to insulin hypoglycemia makes it less likely, but not impossible, that the somatotrope cell is directly responsive to the drug. Although we do not know where methscopolamine is acting to achieve the differential effects reported here on sleep-related and insulin-induced GH secretion, we hypothesize, based on knowledge of the drug's inability to cross the blood-brain barrier, that this action takes place within the mediobasal hypothalamus. A neuronal locus within this general area which is functionally proximal to the final common pathway for GH secretion is suggested. Thus, we would speculate, based on the present results, that one or more pools of cholinergic neurons may abut on portions of the ventromedial or arcuate nuclei, or perhaps on neural elements of the infundibulum, which participate critically in the final common pathway for the regulation of GH secretion in man. Methscopolamine is thus added to a growing list of factors capable of dissociating sleep-related GH secretion and slow-wave sleep (13–22). We conclude that these two phenomena have no necessary neurophysiologic linkage.

Our data demonstrate no effect of methscopolamine on sleep-related PRL secretion. Though an inhibitory cholinergic influence on serum PRL levels in rats has been suggested (40–43), there are no comparable published data in humans. The data presented in this study suggest that the cholinergic system does not play an important role in the regulation of sleep-related PRL secretion in man.

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