Central administration of the somatostatin analog octreotide induces captopril-insensitive sleep responses

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Beranek, L., I. Hajdu, J. Gardi, P. Taishi, F. Obál, J. r., and J. M. Krueger. Central administration of the somatostatin analog octreotide induces captopril-insensitive sleep responses. Am. J. Physiol. 277 (Regulatory Integrative Comp. Physiol.: 46): R1297–R1304, 1999.—The effects of intracerebroventricular injections of the long-lasting somatostatin analog octreotide (Oct) were studied on sleep and behavior in rats. Pyrogen-free physiological saline and Oct (0.001, 0.01, 0.1 µg) or vehicle were administered at light onset, and the electroencephalogram (EEG), motor activity, and cortical brain temperature were recorded during the 12-h light period. Plasma growth hormone (GH) concentrations were measured in samples taken at 30-min intervals after Oct. Oct (0.01 and 0.1 µg) suppressed non-rapid eye movement sleep (NREMS) for 1–2 h. NREMS intensity (delta EEG activity during NREMS) dose dependently increased in hour 3 postinjection and thereafter (0.1 µg). Plasma GH concentrations were suppressed after Oct (0.01 and 0.1 µg), but pulses of GH secretions occurred 90–120 min postinjection in each rat. Oct (0.1 µg) enhanced behavioral activity, including prompt drinking following by grooming, scratching, and feeding. Intracerebroventricular injection of the angiotensin-converting enzyme inhibitor captopril (30 µg, 10 min before Oct), blocked these behavioral responses but not the Oct-induced sleep alterations. The changes in sleep after intracerebroventricular Oct suggest an intracerebral action site and might result from Oct-induced variations in the sleep-promoting activity of GH-releasing hormone.

Several lines of evidence indicate that hypothalamic growth hormone (GH)-releasing hormone (GHRH) promotes non-rapid eye movement sleep (NREMS). Intracerebroventricular injection of GHRH increases NREMS in rats and rabbits (12, 28, 29), and systemic administration of GHRH enhances NREMS in humans (19, 24, 38) and rats (31). Inhibition of endogenous GHRH by means of a competitive antagonist or immunoneutralization decreases sleep (reviewed in Ref. 20). Transgenic mice deficient in the GH-GHRH axis sleep less than their normal littermates (51). The diurnal variations and sleep deprivation-induced changes in hypothalamic GHRH mRNA expression (6, 43) and GHRH content (16) correlate with sleep. Hypophysectomy does not block the NREMS-promoting activity of exogenous GHRH (31). GH is, therefore, not involved in the mediation of GHRH-induced NREMS. In contrast, microinjection of GHRH into the medial preoptic area increases sleep (52). We suggested that stimulation of GH secretion and NREMS are two independent outputs of the hypothalamic GHRHergic neurons (29). The activities of these two outputs are normally synchronized, which explains the temporal association between deep NREMS and GH release (45). The major hypophysiotropic GHRHergic neurons reside in the arcuate nucleus, whereas extra-arcuate GHRHergic neurons around the ventromedial nucleus and in the parvicellular portion of the paraventricular nucleus are implicated in sleep regulation (43). Stimuli that control the hypophysiotropic GHRHergic neurons may also modulate the sleep-promoting GHRHergic activity. Thus high doses of insulin-like growth factor-1 (IGF-1) (32) and GH (26), which act as a negative feedback in the hypothalamus, suppress NREMS. Somatostatin exerts an inhibitory control on GHRH in the hypothalamus (18, 48). Therefore, somatostatinergic stimulation may also decrease NREMS.

Previously, we reported that systemic injection of a long-lasting somatostatin analog, octreotide (Oct), first decreases then increases NREMS (3). In addition, Oct slightly enhanced rapid eye movement sleep (REMS), a result in agreement with previous reports by Dangui and collaborators (9, 10). Somatostatin is a paracrine substance in the gastrointestinal system and inhibits several hormones, some of which have been implicated in sleep regulation. Intracerebroventricular administration of Oct was therefore used in our current experiments to determine whether peripheral or intracerebral action sites mediate the sleep alterations elicited by somatostatinergic stimulation. The advantage of injecting Oct instead of somatostatin is that Oct is 20–75 times more potent as an inhibitor of the somatotropic axis than is somatostatin, and the half-life of Oct is 45–120 min, whereas somatostatin is broken down in minutes (1, 34). Five somatostatin receptors have been cloned: they are termed sst1 to sst5 (there are two sst2 receptors, sst2A and sst2B, as a result of alternative splicing of the sst2 mRNA). Oct is a strong agonist on two somatostatin receptors, sst2 and sst5 receptors, and it has a modest affinity to sst3 receptors (37). Inhibition of the somatotropic axis is attributed to sst2 receptors (35). In the previous experiments with systemic administration of Oct (3), we noted that the injections often elicited drinking. The Oct-elicited behavioral responses were quantified in the current studies. The similarities between some of the responses to Oct and those elicited by angiotensin prompted us to test whether the angiotensin-converting enzyme (ACE) in-

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hibitor captopril can block the effects of Oct on behavior and sleep.

**METHODS**

Animals. Male Sprague-Dawley rats weighing 320–350 g were used. The rats were anesthetized with ketamine-xylazine (87 and 13 mg/kg, respectively), and stainless-steel jewelry screws for electroencephalographic (EEG) recording were implanted over the frontal and parietal cortices and over the cerebellum. A thermistor placed over the parietal cortex served to measure brain cortical temperature ($T_{cr}$). An intracerebroventricular guide cannula was implanted into the left lateral ventricle. The injection needle was inserted into the guide cannula during implantation. The needle extended 0.5 mm beyond the tip of the guide cannula. The drinking response to intracerebroventricular angiotensin (100 ng) was tested 1–2 days after surgery. The rats responding to angiotensin were used in the experiments. After recording, trypan blue was intracerebroventricularly injected and the ventricular system was checked for staining. The data refer to only those rats in which the dye stained both the third and the fourth ventricles and the cerebral aqueduct.

Recording. The rats were housed in individual Plexiglas cages. The cages were placed in recording rooms with a 12:12-h light-dark cycle and with an ambient temperature regulated at 26°C. The rooms were sound attenuated. Food and water were continuously available. The rats were kept in conditions identical to those in the recording rooms for at least 1 mo before the operation. After surgery, the rats were connected to the recording tether and habituated to the experimental conditions for another 7–10 days.

The tethers were attached to commutators. The motor activity of the rats was assessed by recording potentials generated in electromagnetic transducers attached to the tethers. Cables from the commutators and electromagnetic transducers were connected to amplifiers in an adjacent room. The signals were digitized (64-Hz sampling rate) and collected by a computer and stored on compact discs. For scoring, the EEG, $T_{cr}$, and motor activity signals were restored on the computer screen. In addition, power density values were calculated by fast-Fourier transformation for consecutive 8-s epochs in the frequency range 0.25–20.0 Hz for Q, P, delta bands and integrated for 0.5-Hz bins; the spectral resolution was 0.125 Hz. The power density spectra were also displayed on the computer screen. The states of vigilance were determined over 8-s epochs by the usual criteria as NREMS (high-amplitude EEG slow waves, lack of body movements, declining $T_{cr}$ on entry), REMS (highly regular theta activity in the EEG, general lack of body movements with occasional twitches, and a rapid rise in $T_{cr}$ at onset), and wakefulness (EEG activities similar to but often less regular and with lower amplitude than those in REMS, frequent body movements, and a gradual increase in $T_{cr}$ after arousal). The percentage of the time spent in each state of vigilance over 1-h periods was determined. The 8-s $T_{cr}$ values were averaged for 1-h periods. Mean power density spectra were calculated for 8-s uninterrupted periods of artifact-free NREMS in each hour. The power density values for the 0.25- to 4-Hz (delta) frequency range were integrated and used as an index of EEG slow-wave activity (SWA) during NREMS to characterize sleep intensity in each recording hour. In the rats injected with the highest dose of Oct, the power of the EEG delta waves was also calculated for wakefulness for the first 6 h of the recording on the baseline day and after Oct (epochs of drinking and eating were left out from the calculations).

Treatments. Oct (Sandostatin injection, 0.1 µg/µl; Novartis Pharma, Basel, Switzerland) was intracerebroventricularly injected in a volume of 2 µl. Three groups of rats received Oct before light onset in doses as follows: 0.001 ($n = 7$), 0.01 ($n = 11$), and 0.1 µg ($n = 11$). The Sandostatin injection was diluted in pyrogen-free physiological saline (PFS). One group of rats ($n = 8$) received the vehicle (2 µl) of the Oct injection in the same dilution as the 0.1 µg Oct. The vehicle containing lactate and mannitol was donated by Novartis Pharma, Basel, Switzerland. Each rat was tested with only one dose of Oct in the sleep experiments. The rats were recorded for 12 h on 2 consecutive days: a baseline day when 2 µl PFS was administered and an experimental day when Oct or the vehicle was injected. In each group, approximately one-half of the rats received PFS on day 1 and Oct or vehicle on day 2, whereas the order of the baseline day and experimental day was reversed for the rest of the animals. The rats were injected 10–15 min before light onset. The recording started at light onset and continued for 12 h. The pH of both the Oct and vehicle was 3.8–4.0.

Seven rats were used to determine the effects of the ACE inhibitor captopril (30 µg in 2 µl) on the Oct (0.1 µg)-induced sleep alterations. These rats were recorded for 3 days when they received double intracerebroventricular injections as follows: PFS+PFS (baseline), captopril+PFS, and captopril+PFS. The order of the sessions varied. Captopril was administered 15 min before the next injection (PFS or Oct), whereas the rats received two PFS injections 15 min apart on the baseline day. The protocol of sleep recording was the same as that used to test the various doses of Oct.

Behavioral testing. It was evident in the sleep studies that intracerebroventricular Oct activated specific behavioral patterns: the rats regularly drank water immediately after the injections. To quantify the behavioral responses to Oct, the behavior of 12 rats was scored at 30-s intervals for 45 min after double injections of PFS+PFS, PFS+Oct, and captopril+Oct on 3 different days. The order of the sessions varied. At 30-s intervals, the momentary behavior of each rat was classified in one of the categories as follows: drinking, feeding, grooming, scratching, exploring, and lying (irrespective whether rats slept or were obviously awake). In a separate group of rats, behavioral scores were recorded after the administrations of captopril and the vehicle of Oct. The behavior of these rats did not differ from that observed after PFS+PFS, and, therefore, the data are not reported herein.

Determination of GH. The rats already implanted with an intracerebroventricular cannula received a Silastic cardiac catheter. The catheter was introduced into the right atrium via the right external jugular vein 4–7 days before blood sampling. The rats were housed individually in environmental chambers. Silastic tubing was connected to the cardiac catheters, and the tubing was routed out of the chambers through holes in the wall. Thus the rats could move freely, and they were not disturbed by the sampling. The rats received 0.01 ($n = 7$) or 0.1 µg Oct ($n = 9$) on the experimental day and PFS on the baseline day. The intracerebroventricular injections were performed at light onset. Blood sampling started 30 min after light onset and continued for 5 h at 30-min intervals. Each blood sample was 150–200 µl. The blood was centrifuged, and the plasma was stored at −20°C until assay. The red blood cells were reconstituted in physiological saline and reinjected. GH was determined in a single radioimmunoassay in duplicates. The intra-assay coefficient of variation was <7%. The immunoreagents (rat GH antiserum: GH-S-5; iodination grade rat GH: GH-I-6; and standard: rat GH RP-2) were provided by The National Hormone and Pituitary Program, National Institute of Diabetes and Digestive and Kidney Diseases.
Statistics. The hourly values of the states of vigilance, SWA, and Tcrt during the 12-h recording periods were compared by means of two-way ANOVA for repeated measures between the baseline and the experimental days or among the 3 days of recording in the studies with captopril and Oct. The treatment effect and the time effect (variations across the individual hours) were the two factors of the ANOVA. In general, the F statistics are only provided for the treatment effect and for the interactions between the treatment and the time factors when statistically significant differences are noted, and significant variations in time are not discussed. Significant changes in sleep in hour 1 postinjection were determined by means of the paired t-test. The nonparametric Friedman repeated-measures ANOVA on ranks was used to determine the differences in the frequency of the occurrences of individual behavioral scores among the three treatments. The effects of Oct on plasma GH concentration were analyzed by means of ANOVA for repeated measures. Intergroup differences (groups injected with various doses) in the changes in SWA were evaluated by one-way ANOVA for independent samples. When several groups or more than two treatments were compared, the Student-Newman-Keuls test was used for post hoc analysis to identify which group and treatment differed from the other groups and treatments. An α-level of P < 0.05 was considered to be significant in all tests.

RESULTS

Effects of Oct on sleep. Duration of NREMS was high at the beginning of the light period and declined toward dark onset after intracerebroventricular PFS in each group of rats (Fig. 1). The 0.001-µg dose of Oct failed to alter NREMS. Calculating for the 12-h light period, NREMS also did not differ between the baseline day and the experimental day in the rats injected with 0.01 µg Oct. There was, however, a significant interaction between the treatment factor and the time factor after 0.01 µg Oct [F(1,1110) = 3.548], indicating differences in the time courses of the hourly duration of NREMS between the 2 days of recording. NREMS decreased significantly (t-test) in hour 1 postinjection after 0.01 µg Oct (Fig. 1). The high dose of Oct markedly suppressed NREMS in hour 1 and hour 2 postinjection (t-test). Thereafter, NREMS tended to increase above baseline. The different courses of the hourly duration of NREMS on the 2 days resulted in a significant interaction between the treatment and the time factors [F(1,1110) = 10.540], but the total duration of NREMS during the 12-h recording was not altered after 0.1 µg Oct. Intracerebroventricular injection of the vehicle did not alter NREMS.

After a 2-h latency, Oct significantly promoted SWA during NREMS (Fig. 1). A tendency of enhanced SWA could already be observed after 0.001 µg Oct, and the increases in SWA became marked after 0.01 µg Oct in hour 3 postinjection. There was a significant interaction between the treatment factor and the time factor after 0.01 µg Oct [F(1,1110) = 1.99], although changes in SWA did not reach the level of statistical significance when calculated for the 12-h light period. Administration of 0.1 µg Oct enhanced SWA over a period of several hours, resulting in significant differences between the baseline and the experimental days [F(1,8) = 8.96]. The time courses of hourly SWA also differed between the 2 days (treatment × time interaction: F(1,118) = 3.94). The Oct-induced alterations in SWA displayed significant dose-response relationships [F(2,345) = 22.6], with significant differences between the responses to each dose of Oct (Student-Newman-Keuls test). Injection of the vehicle did not alter SWA. Compared with baseline, the mean changes in SWA during wakefulness varied between 3.5 ± 3.4% (hour 1) and −3.9 ± 3.6% (hour 4) without statistically significant differences or pattern after 0.1 µg Oct. Intracerebroventricular injections of 0.001 and 0.1 µg Oct or the vehicle failed to alter REMS (Fig. 1). A tendency for REMS to increase could be observed during the last hours of the light period after 0.1 µg Oct, but these changes did not reach the level of statistical significance.
Normally, Tcrt decreases after light onset for 2–3 h and then increases toward the end of the light period. In our rats, however, a moderate (0.5°C) rise in Tcrt occurred after intracerebroventricular administration of both PFS and Oct or the vehicle (Fig. 1). The hyperthermia elicited by intracerebroventricular injections of saline, vehicle, and the various doses of Oct did not differ. Tcrt peaked between 4 and 6 h postinjection and declined thereafter.

Effects of Oct on GH. On the baseline day, surges of GH secretion were regularly observed 30–90 min after light onset. Oct inhibited GH secretion for 60–90 min. Then a temporary rise in plasma GH concentration occurred in each rat (Fig. 2). Plasma GH peaked at 90 and 120 min postinjection after 0.01 and 0.1 µg Oct, respectively (Fig. 3). There were significant differences in the time courses of the variations in plasma GH concentrations between the baseline and the experimental days after 0.01 µg Oct [treatment x time interaction: F(9,54) = 5.90], but GH concentrations calculated for the 5-h sampling period did not differ between the 2 days. GH concentrations were significantly suppressed after 0.1 µg Oct [F(1,8) = 33.95], and the interaction between the treatment and time factors were also significant [F(9,72) = 3.08].

Effects of Oct on behavior. The predominant behavioral sequence after intracerebroventricular injection of PFS included exploration, grooming, and finally rest. After 10–15 min postinjection, the rats spent most of the time in behavioral rest, often sleeping. Oct elicited vigorous drinking (Fig. 4). Bouts of drinking, interrupted by scratching and grooming, recurred many times during the first 10 min. Although drinking subsided thereafter, the rats remained active, displaying grooming, scratching, and exploration. Feeding increased gradually after the first 10 min, and each rat exhibited long periods of eating toward the end of the 45-min observation period. Captopril significantly inhibited both Oct-induced drinking and feeding. The Friedman test indicated significant differences in drinking (χ² = 19.5) and feeding (χ² = 11.0) among the three treatments, with different scores after PFS+Oct than after both PFS+PFS and captopril+Oct (Student-Newman-Keuls test). The occurrences of feeding and drinking did not differ after PFS+PFS and captopril+Oct. The scores of grooming, scratching, and exploring were pooled in Fig. 4 as “general activity.” There were no differences in general activity among the 3 days. Nevertheless, Oct significantly enhanced the frequency of grooming, and there was a tendency for scratching to increase at the expense of exploring. These effects were inhibited by pretreatment with captopril (not shown). The frequency of the occurrence of lying differed significantly among the days (χ² = 13.2). Oct significantly decreased rest (Student-Newman-Keuls test). Although the occurrence of lying did not differ between the PFS+PFS and the captopril+Oct days, qualitatively the rats’ behavior was not the same. After captopril+Oct, the lying rats seemed restless, displaying frequent shifts in body position.

Effects of Oct on sleep after pretreatment with captopril. Sleep and Tcrt after intracerebroventricular injection of PFS+PFS did not differ from sleep and Tcrt after single PFS injections (Figs. 1 and 5). Captopril (captopril+PFS) did not alter sleep or SWA during NREMS. Intracerebroventricular Oct significantly sup-
pressed NREMS in hour 1 postinjection (t-test) in the captopril-pretreated rats, and NREMS was also below baseline in hour 2 postinjection (Fig. 5). These changes in NREMS were similar to those observed after 0.1 µg Oct without captopril administration. Calculated for the 12-h light period, duration of NREMS did not differ among the 3 days. In contrast, the interaction between the treatment and time factors was significant among the 3 days. In agreement with Danguir and collaborators (9, 10), Somatostatin is implicated in the genesis of hyperthermia (23). In our experiments, however, the changes in NREMS after intracerebroventricular injection replicate those observed after systemic injection of Oct. Nevertheless, peripheral action sites should also be considered after intracerebroventricular Oct injection, because somatostatin leaks out of the cerebral ventricles into the systemic circulation (40). With the possible exception of the anterior pituitary, however, it is unlikely that the intracerebroventricularly injected small doses of Oct can result in plasma Oct concentrations comparable to those after systemic administration. In the pituitary, it is possible that the inhibition of GH secretion is in part a direct effect of intracerebroventricular Oct on the pituitary somatotropes. Suppression of GH by means of immunoneutralization is associated with decreases in NREMS and particularly in SWA in the rat (30). These changes are, however, modest (10% recording time) and develop relatively slowly. The alterations in NREMS elicited by intracerebroventricular Oct are, therefore, attributed to intracerebral actions of Oct.

In agreement with Danguir and De Saint-Hilaire's findings (10), REMS was enhanced in response to systemic administration of Oct in our previous experiments (3). The intracerebroventricularly administered Oct, however, failed to exhibit such activity. After each injection (PFS, Oct, captopril, vehicle), duration of REMS was relatively low for 6 h. The period of suppressed REMS corresponded to the rises in Tcrt. It is possible that the hyperthermia blocked the REMS-promoting activity of Oct.

Somatostatin is implicated in the genesis of hyperthermia (23). In our experiments, however, the changes in Tcrt did not depend on the treatment (PFS, Oct, vehicle, captopril) or on the dose of Oct. The hyperthermia is, therefore, attributed to the intracerebroventricu-
lar injection itself. A possible explanation is that slight tissue damage was caused by the volume of the injection or by the needle extending beyond the tip of the guide cannula. Tissue damage is associated with releases of endogenous pyrogens, cytokines, that elicit fever. Cytokines such as interleukin-1 also enhance NREMS (21). However, if the intracerebroventricular injections in fact activated the cytokine network, then this occurred on both the baseline days and the experimental days. Thus the Oct-induced alterations in NREMS are not due to the mechanism underlying the rise in Tcrt. This conclusion is supported by the fact that systemic injections of Oct do not affect Tcrt (3), yet they elicit the same changes in NREMS as those observed after intracerebroventricular administration of Oct.

Several lines of evidence indicate that hypothalamic GHRH promotes physiological sleep. Somatostatin inhibits both the actions and the release of GHRH (18, 48). The intra-arcuate GHRH neurons are modulated predominantly by local somatostatinergic interneurons. The periventricular hypophysiotropic somatostatinergic neurons receive input from the GHRH-containing neurons residing outside of the arcuate nucleus (4). The somatostatinergic control of the extra-arcuate GHRHergic neurons, which are implicated in sleep regulation, is not clear, but it may occur via interneurons. In addition, somatostatin may also modulate GHRH actions in those basal forebrain structures that mediate the effects on sleep. Irrespective of the ultimate mechanism, that the reciprocal interaction between hypothalamic GHRH and somatostatin, which is well known in endocrinology, also works in sleep regulation is indicated by a recent observation: sleep-deprivation induced stimulation of hypophysiotropic GHRH mRNA expression is associated with simultaneous suppression in somatostatin mRNA, and these changes occur in nonhypophysiotropic neurons (50). Inhibition of GHRH by Oct may, therefore, mediate the decreases in NREMS in our experiments.

The suppression of the somatotropic axis by Oct is attributed to a stimulation of sst2 receptors (35). These receptors, which mediate both postsynaptic and presynaptic actions of somatostatin (11), are distributed throughout the brain (41). Intracerebroventricularly injected Oct may mimic somatostatin in a number of actions sites unrelated to GHRH, and these effects of Oct may also alter sleep. Intracerebroventricular administration of somatostatin elicits grooming (46), stimulates food intake (13), and induces vasopressin secretion and a rise in blood pressure (7). We describe here a previously unreported response to somatostatinergic stimulation: drinking. These effects of Oct were, however, blocked by captopril (captopril also inhibits the Oct-elicited rise in blood pressure and vasopressin secretion; unpublished observations). Captopril blocks the formation of angiotensin by inhibiting ACE, but it may also interfere with the metabolism of other peptides such as bradykinin and substance P (49). Our recent experiments indicate that intracerebroventricular injections of the angiotensin receptor blocker saralasin also inhibit the drinking response to Oct, i.e., the effect is in fact mediated by angiotensin. Captopril, however, did not interfere with the sleep alterations elicited by Oct. These results, of course, do not prove that the changes in sleep involve alterations in GHRHergic activity, but at least they indicate that they cannot be due to Oct-induced behavioral responses, which seem to involve intracerebral angiotensin.

The late increase in the NREMS-associated SWA is a prominent response to both intracerebroventricular and systemic Oct. Stimulation of SWA is a dose-related effect of Oct and occurs consistently in various groups of rats. SWA is a measure of NREMS intensity, and increases in SWA during NREMS indicate promotion of sleep (5). Although NREMS decreased in hours 1 and 2 after 0.1 µg Oct, the stimulation of SWA cannot be attributed to sleep loss because a 1- to 2-hr sleep deprivation is not sufficient to elicit such a response (42), although enhancements in SWA occurring after long-

![Fig. 5. Effects of intracerebroventricular captopril (30 µg) on Oct (0.1 µg)-induced sleep alterations during 12-h light period. Rats (n = 7) received 2 intracerebroventricular injections of PFS + PFS (○), captopril + PFS (△), and Capt + Oct (▲) with 15 min in between the 2 injections on 3 different days. For SWA, deviations from baseline (PFS + PFS) are shown (solid bars: captopril + Oct, open bars: captopril + PFS). A: SWA; B: NREMS; C: REMS; D: Tcrt.](http://ajpregu.physiology.org/doi/abs/10.1152/ajpregu.00201.2016)
term sleep deprivation may be larger (14). The magnitude of the increments in delta power during NREMS after Oct is comparable to the SWA response to sleep-promoting doses of interleukin-1 during the light cycle in the rat (33) or to the increases in delta power elicited by preoptic heating in the cat (25). In these cases, the stimuli elicit SWA responses superimposed on the normal homeostatic regulation and the enhancements in NREMS intensity occur without significant increases in NREMS duration.

The mechanism of the Oct-elicited increases in SWA is not known, but there may be similarities between the GHRH-somatostatin regulation of endocrine function and GHRH-somatostatin regulation of sleep. In the somatotropic axis, somatostatin not only inhibits GH secretion but also has an important role in the maintenance or facilitation of rat pituitary responsiveness to GHRH. In addition to promoting an accumulation in the intracellular GH store, somatostatin may prevent the desensitization or downregulation of GHRH receptors, it may enhance the synthesis of GHRH receptors, or it may alter the second messenger system mediating GHRH actions (44, 47). Withdrawal of somatostatinergic stimulation induces GHRH release (27) and increases in GH secretion to endogenous (8, 39) or exogenous GHRH (39). In rats, GH secretion elicited by exogenous GHRH is significantly augmented 3 h after systemic Oct injection (44). Surges of GH secretion were regularly observed 90–120 min after Oct in our experiments, indicating that the Oct-induced inhibition of the somatotropic axis definitely vanished when SWA increased. If the sleep-promoting GHRH neurons or GHRH-responsive structures are similarly modulated by somatostatin as the hypophysiotorpic GHRH neurons and the pituitary somatotropes, then the increases in SWA might be mediated by a reboundlike enhancement in GHRH release or increased sensitivity to GHRH in the preoptic region, the area that mediates the sleep-promoting activity of GHRH (52).

In conclusion, intracerebroventricularly administered Oct elicits an immediate suppression of NREMS followed by enhancements in SWA during NREMS, a sign of stimulation of sleep. These sleep alterations correspond to those observed after systemic injection of Oct. Although the Oct-induced changes in NREMS are consistent with the possible Oct-elicited variations in GHRHergic activity further experiments are needed to elucidate the role of GHRH in the sleep responses. Regardless, our experiments indicate that the stimulation of the intracerebral angiotensinergic mechanisms by Oct are not involved in Oct-induced sleep alterations.

Perspectives

Current findings together with previous observations that high doses of GH (26) and IGF-1 (32) inhibit sleep collectively suggest that negative feedback mechanisms in the somatotropic axis not only inhibit GH secretion but also suppress sleep. This further stresses the intimate relationship between sleep and GH regulation and opens up the possibility that a significant portion of the knowledge accumulated concerning the regulation of GH secretion might be applicable to sleep.

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