Sleep of transgenic mice producing excess rat growth hormone

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Hajdu, I., F. Obal, Jr., J. Fang, J. M. Krueger, and C. D. Rollo. Sleep of transgenic mice producing excess rat growth hormone. Am J Physiol Regulatory Integrative Comp Physiol 282: R70–R76, 2002.—The effects of chronic excess of growth hormone (GH) on sleep-wake activity was determined in giant transgenic mice in which the metallothionein-1 promoter stimulates the expression of rat GH (MT-rGH mice) and in their normal littermates. In the MT-rGH mice, the time spent in spontaneous non-rapid eye movement sleep (NREMS) was enhanced moderately, and rapid eye movement sleep (REMS) time increased greatly during the light period. After a 12-h sleep deprivation, the MT-rGH mice continued to sleep more than the normal mice, but there were no differences in the increments in NREMS, REMS, and electroencephalogram (EEG) slow-wave activity (SWA) during NREMS between the two groups. Injection of the somatostatin analog octreotide elicited a prompt sleep suppression followed by increases in SWA during NREMS in normal mice. These changes were attenuated in the MT-rGH mice. The decreased responsiveness to octreotide is explained by a chronic suppression of hypothalamic GH-releasing hormone in the MT-rGH mice. Enhancements in spontaneous REMS are attributed to the REMS-promoting activity of GH. The increases in spontaneous NREMS are, however, not consistent with our current understanding of the role of somatotropic hormones in sleep regulation. Metabolic, neurotransmitter, or hormonal changes associated with chronic GH excess may indirectly influence sleep.

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Regulation of sleep and the activity of the somatotropic system are intimately related. Deep non-rapid eye movement sleep (NREMS) is associated with a major surge of growth hormone (GH) release in humans, particularly in males (44, 50). Links between NREMS and GH secretion have also been reported in many other species (reviewed in Ref. 52). Of the members of the somatotropic system, GH-releasing hormone (GHRH) exhibits well-documented NREMS-promoting activity in rats, rabbits, and humans (13, 20, 28, 38, 48). Stimulation of GH secretion and promotion of NREMS are parallel and independent but dissociable outputs of hypothalamic GHRHergic neurons mediated by the anterior pituitary and the medial preoptic region, respectively (31, 55). Somatostatin, which inhibits both GHRH and GH release, also inhibits NREMS (4, 5) and may stimulate REMS (7). The effects on sleep are less clear for GH and insulin-like growth factor-1 (IGF-1). The most consistent finding with GH is that it promotes REMS after acute administration (9, 25, 49). Exogenous IGF-1 may stimulate NREMS when the dose is low (33). Both GH and IGF-1 feed back to inhibit GHRH, and acute injections of high doses of these hormones also inhibit NREMS (25, 34).

Transgenic and mutant animals provide models for studying sleep in conditions with chronic alterations in the somatotropic system. Permanent decreases in NREMS were found in transgenic mice with GHRH deficiency (54) and in mutant rats with a defect in the GHRH receptor signaling mechanism (30). A behavioral study suggests that sleep time is increased in giant transgenic mice in which the metallothionein-1 promoter stimulates expression of rat GH (MT-rGH mice) (23). The MT-rGH mice also display hypoactivity during wakefulness. These mice express plasma GH levels 100–800 times normal, and IGF-1 is elevated two- to threefold (24, 37). The GH concentration in the plasma is permanently elevated; there are no secretion pulses. The high levels of GH and IGF-1 are associated with decreases and increases in hypothalamic GHRH and somatostatin productions, respectively. ACTH, corticosterone, and prolactin secretions are enhanced, whereas plasma follicle-stimulating hormone levels are suppressed in mice with excess GH secretion (3). The aim of the current experiments was to determine spontaneous sleep, the sleep responses to sleep deprivation (SD), and the effects on sleep of the long-acting somatostatin analog octreotide in the MT-rGH mice.

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METHODS

Animals: surgery. The transgene in MT-rGH mice is a fusion gene composed of the promoter region of the mouse metallothionein-1 gene and the coding region of the rat GH (rGH) gene (37). The mice have multiple copies of the fusion genes incorporated into one chromosome. The transgene is expressed in various organs, but the liver is a major source of GH. Production and secretion of the transgenic GH are not subjected to normal regulation by GHRH and somatostatin (3). The original transgenic stock of MT-rGH mice included C57BL/6J male x SJL female hybrids at McMaster University. Original stock was donated by Dr. R. Brinster (Univ. of Pennsylvania). Breeding normal females to heterozygously transgenic males yields equal proportions of transgenic and normal offspring with similar genetic background. Fifteen normal (control) and 14 MT-rGH male mice were used. The mice were 5–6 mo old at the time of the experiments. The body weight of the normal and MT-rGH mice was 30.4 ± 0.31 and 50.3 ± 3.17 g, respectively, with significant differences (Student’s t-test, Pr < 0.05) between the two groups.

Three electrodes were implanted into the skull under ketamine-xylazine anesthesia (87 and 13 mg/kg, respectively). The electrodes consisted of stainless steel wires, and they were placed on the top of the dura mater over the frontal and parietal lobes and the cerebellum. These electrodes served to record the electroencephalogram (EEG). Two stainless steel wires were inserted into the dorsal neck muscles to record the electromyogram (EMG). The EEG and EMG electrodes were connected to a pedestal implanted on the top of the skull. The surgeries were performed 7–10 days before recording.

Recording. The mice were housed in individual Plexiglas cages at an ambient temperature of 24°C. The light-dark cycle consisted of 12 h of light and 12 h of dark. Food and water were continuously available. The mice were connected to lightweight recording cables and habituated to the experimental conditions for 5–6 days. The cables were attached to commutators. Cables from the commutators were connected to amplifiers. The signals were digitized (128-Hz sampling rate) and collected by a computer and stored on compact discs. For scoring, the EEG and EMG were restored on the computer screen. In addition, power density values were calculated by fast-Fourier transformation for consecutive 10-s epochs in the frequency range 0.25–40.0 Hz for 0.5-Hz bands. The power density spectra were also displayed on the computer screen. The states of vigilance were determined for 10-s epochs by the usual criteria as NREMS (high-amplitude EEG slow waves and low-tone muscle activity), REMS (high regular theta EEG activity and loss of muscle tone with occasional twitches), and wakefulness (EEG activities similar to but often less regular and with lower amplitude than those in REMS and high-EMG activity). The percentage of the time spent in each state of vigilance for 1-h periods was determined. Mean power density spectra were calculated for 10-s uninterrupted periods of artifact-free NREMS in each hour. The power density values for the 0.5- 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.

Experimental schedule. After habituation, the sleep-wake activity of mice was recorded for 2 consecutive days starting at light onset. Eight normal and 10 MT-rGH mice were sleep deprived on day 3 during the 12 h of the light period. Recordings from the mice were also made during SD. The recording continued for 36 h after SD (dark-light-dark periods, 12 h each). SD was performed by gentle handling while the mice stayed in their home cage; whenever behavioral or EEG signs of sleep were observed, the mice were aroused by knocking on the cage or touching them. The effects of the somatostatin analog octreotide were tested in 10 normal and 11 MT-rGH mice. Of the mice tested with octreotide, 3 control mice and 10 MT-rGH mice also participated in the experiments with SD; these experiments were separated by at least 4 days. The mice received 100 μg/kg octreotide (Sandostatin injection, Novartis Pharma, Basel) subcutaneously on the experimental day and the same volume of the vehicle (donated by Novartis Pharma) on the baseline. The sequence of the baseline and the experimental days varied. The injections were performed 5–10 min before light onset, and sleep-wake activity was recorded during the 12-h light period and during 11 h of the subsequent dark period.

Statistics. Data (hourly values of the states of vigilance, and SWA during NREMS) obtained on the 2 days of undisturbed recording did not differ and were averaged to characterize spontaneous sleep-wake activity in the normal and the MT-rGH mice. These variables during the light and dark periods were compared by means of two-way ANOVA between the two groups. The group effects (independent samples) and the time effects (repeated measures) were the two factors of the ANOVA. ANOVA was also used to evaluate the effects of SD and octreotide on the sleep parameters within each group and to compare the SD-induced changes in these variables between groups. Mice are often awake for long time periods during darkness, which may result in missing values of SWA when SWA during NREMS is determined in individuals. After SD, however, each mouse had NREMS in each hour of the recording, and periods of NREMS occurred in each hour in at least one of the baseline nights in each mouse. Thus there were no missing SWA values in the current experiments. Because variations in sleep with time of day are well documented, only the group effects are discussed herein, and F statistics for variations in time are not presented. NREMS in hour 1 after the injections of octreotide and the vehicle was compared by means of the paired t-test, whereas the Student t-test was used for intergroup comparison of the same variable. An a-level of P < 0.05 was considered to be significant in all tests.

RESULTS

Spontaneous sleep. The control and MT-rGH mice displayed the normal diurnal variations of sleep-wake activity with higher amounts of time spent in NREMS and REMS in the light period than in the dark period (Fig. 1). SWA during NREMS peaked at light onset, declined during the day, and increased at night.

The time spent in NREMS was consistently and modestly higher in the MT-rGH mice than in the normal mice during the light period (F(1,27) = 13.11, P < 0.005) (Fig. 1, Table 1). The differences between the groups varied with the time [F(11,347) = 5.06, P < 0.0001] and were more obvious in the second half than in the first half of the light period. NREMS time did not differ significantly between the MT-rGH and normal mice at night. In the light period, the mean duration of uninterrupted NREMS bouts was significantly longer in the MT-rGH mice than in the normal mice (1.67 ± 0.08 vs. 1.29 ± 0.05 min, P < 0.005), whereas the number of the uninterrupted NREMS bouts (248.3 ± 9.75 vs. 223.9 ± 10.44) did not differ significantly between the groups. SWA during NREMS was not altered in the MT-rGH mice.
The time spent in REMS almost doubled in the MT-rGH mice particularly during the second portion of the light period (Fig. 1). Both the group effects and the group × time interaction were statistically significant \( F(1,27) = 16.09, P < 0.001 \) for NREMS; \( F(1,1347) = 2.47, P < 0.0001 \) (Table 1). The MT-rGH mice had a significantly higher number of REMS bouts than the normal mice (44.2 ± 1.97 vs. 31.9 ± 2.71, \( P < 0.005 \)), but the mean duration of uninterrupted REMS epochs did not differ between the groups (1.65 ± 0.03 and 1.62 ± 0.05 min). REMS was normal in the MT-rGH mice at night.

Response to SD. The 12-h sleep loss elicited robust increases in NREMS and REMS during the subsequent night in both groups of animals [normal mice: \( F(1,7) = 33.35, P < 0.001 \) for NREMS; \( F(1,7) = 17.04, P < 0.005 \) for REMS; MT-rGH mice: \( F(1,9) = 83.53, P < 0.0001 \) for NREMS; \( F(1,9) = 58.77, P < 0.0001 \) for REMS] (Fig. 2, Table 1). The time spent in NREMS and REMS was significantly greater in the MT-rGH mice than in the controls during the 12-h dark period after SD [NREMS: \( F(1,16) = 0.95, P < 0.05 \); REMS: \( F(1,16) = 7.54, P < 0.05 \)]. The increments in NREMS and REMS, however, did not differ between the groups. SWA during NREMS was enhanced by ~80% in hour 1 after SD in both groups of mice. Thereafter, SWA declined rapidly and was slightly below baseline at the end of the night. The changes in SWA were significant in both groups [controls: \( F(1,7) = 17.23, P < 0.005 \); MT-rGH mice: \( F(1,9) = 17.23, P < 0.005 \)] and varied with time [controls: \( F(11,77) = 25.25, P < 0.0001 \); MT-rGH mice: \( F(11,99) = 25.25, P < 0.0001 \)] without differences between the normal and the MT-rGH mice.

The times spent in NREMS and REMS were not altered during the light period subsequent to the recovery night (Table 1). SWA tended to decrease below baseline in both groups, but these changes did not reach statistical significance. NREMS, REMS, and SWA did not differ from baseline during the night of the post-SD day (Table 1).

Effects of octreotide. Injection of octreotide was followed by prompt and marked suppression of NREMS in hour 1 of the light period in the normal mice (\( P < 0.01 \), paired \( t \)-test) (Fig. 3). Duration of NREMS approached baseline in hour 2 and was normal during the subsequent 10 h of the light period (Table 1). ANOVA failed to reveal significant changes in NREMS across the 12-h light period although the treatment × time interaction was significant \( F(11,99) = 3.37, P < 0.05 \), indicating differences in the time courses of the hourly duration of NREMS between the 2 days. Starting in hour 2, SWA during NREMS was enhanced and remained above baseline until the end of recording (Fig. 3). The changes in SWA, calculated for hours 2–12, were statistically significant \( F(1,9) = 9.86, P < 0.05 \). REMS was not altered after octreotide.

Octreotide also elicited decreases in NREMS in hour 1 postinjection in the MT-rGH mice (\( P < 0.01 \), paired \( t \)-test) (Fig. 3). Nevertheless, the time spent in NREMS

| Table 1. NREMS and REMS in normal and MT-rGH mice on baseline day, after 12-h SD carried out during the light period, and after injection of octreotide at light onset |
|-----------------|-----------------|-----------------|-----------------|
|                 | Light           | Dark            |                 |
|                 | Normal MT-rGH   | Normal MT-rGH   |                 |
|                 | NREMS, % recording time |          |                 |
| Baseline        | 42.7 ± 1.13     | 48.6 ± 1.12*    | 26.6 ± 1.53     |
| SD night        | 41.3 ± 1.37†    | 47.9 ± 2.06**†  | 25.7 ± 2.04     |
| Post-SD day     | 42.8 ± 2.44     | 47.9 ± 1.21*    | 28.9 ± 1.89     |
| Octreotide (100 μg/kg sc) | 42.7 ± 0.90     | 47.8 ± 1.55*    | 28.3 ± 1.82     |
|                 | 29.2 ± 2.14     |                 |                 |
| NREMS, % recording time |          |                 |                 |
| Baseline        | 7.0 ± 0.51      | 9.8 ± 0.43*     | 4.9 ± 0.46      |
| SD night        | 8.6 ± 0.54†     | 10.7 ± 1.57**†  | 5.0 ± 0.56      |
| Post-SD day     | 8.0 ± 0.64      | 10.5 ± 0.51*    | 5.1 ± 0.71      |
| Octreotide (100 μg/kg sc) | 7.3 ± 0.51     | 9.5 ± 0.39*     | 5.0 ± 0.48      |
|                 | 5.3 ± 0.62      |                 |                 |

Values are means ± SE of non-rapid eye movement sleep (NREMS) and rapid eye movement sleep (REMS) percent recording times. Baseline: \( n = 15 \) normal mice and 14 giant transgenic mice in which the metallothionein–1 promoter stimulates expression of rat growth hormone (MT-rGH mice); sleep deprivation (SD) night and post-SD day: \( n = 8 \) normal and 10 MT-rGH mice; octreotide: \( n = 10 \) normal and 11 MT-rGH mice. *Significant difference between normal and MT-rGH mice (group effects ANOVA). †Significant difference compared with respective baseline (each rat compared with its own baseline; group effects of ANOVA with repeated measures).
remained significantly higher in the MT-rGH mice than in the normal mice (MT-rGH: 25.5 ± 4.24%; normal: 12.4 ± 3.46%; P < 0.05, Student t-test) although NREMS did not differ between the groups after administration of the vehicle in hour 1 on the baseline day (MT-rGH: 41.3 ± 3.58%; normal: 38.8 ± 6.26%). A significant treatment × time interaction was also noted in NREMS across the 12 h in the MT-rGH mice [F(11,110) = 3.4, P < 0.0005]. REMS did not change after octreotide. In contrast to the normal mice, the MT-rGH mice exhibited only a weak tendency of enhancement in SWA during NREMS (Fig. 3). These changes did not reach the level of statistical significance although the treatment × time interaction was statistically significant [F(10,100) = 4.71, P < 0.0001, hours 9–12]. The octreotide-induced SWA responses differed significantly between the normal and the MT-rGH mice [F(1,19) = 5.73, P < 0.05], and the differences varied with the time [group × time interaction: F(10,190) = 2.41, P < 0.01].

Sleep was not altered during the subsequent dark period in normal or MT-rGH mice.

**DISCUSSION**

Current findings confirmed previous behavioral observations in that the MT-rGH mice spent more time sleeping than normal mice. Although the increments in NREMS were modest, 5.9% recording time, this change in NREMS time yielded 42 min of extra sleep in the 12-h light period. Nevertheless, REMS seemed to be the state of sleep that was particularly enhanced in the MT-rGH mice. The time spent in REMS doubled in the last quarter of the light period. MT-rGH mice acquire a spatial memory task at nearly twice the rate of their normal siblings (43). Such tasks require memory consolidation that might be promoted by sleep. Both NREMS and REMS have been implicated in memory processes (6), and REMS correlates with learning abilities across mouse strains (36).

Enhancements in REMS in the MT-rGH mice are in line with previous findings suggesting a REMS-promoting activity for GH. Acute injections of GH elicit increases in REMS in rats (9), cats (49), and humans (25), and an acute withdrawal of GH is followed by decreases in REMS in rats (29). GH-deficient children exhibit less REMS than aged-matched controls, but REMS is not altered in adults with GH deficiency (1, 16, 35, 53). A decreased REMS time was, however, reported in acromegalic adults producing extra GH (2), suggesting that the REMS-promoting activity of GH might depend on age and/or species. Rats with impairment in the GHRH signaling pathway have less REMS than normal rats, and the decreases in REMS are attributed to the low GH production (30). In contrast,
transgenic mice that produce GH in the brain and thus have a GHRH deficiency have normal REMS (54). The mechanism by which GH may stimulate REMS is not clear, however. GH has access to the brain in part via retrograde circulation in the pituitary portal veins and in part via specific transporters residing in the choroid plexus (reviewed in Ref. 27). GH is capable of stimulating IGF-1 production in the hypothalamus, and this IGF-1 is involved in GH-induced negative feedback on GHRH (45). It is unlikely, however, that IGF-1 contributes to stimulation of REMS because intracerebral administration of IGF-1 fails to elicit consistent REMS responses (33). GH may modulate neurotransmission and enzyme activity in the brain (26). Signs of altered dopaminergic and noradrenergic transmission have been reported in transgenic mice producing excess GH (46, 47). Increases in REMS occur 2–3 h after an acute injection of GH, suggesting an indirect action (9). Drucker-Colin et al. (9) found that the GH-induced enhancements in REMS were associated with increases in protein synthesis in the brain stem, and inhibitors of protein synthesis blocked REMS response to GH. The REMS-promoting activity of GH is similar to the effects on REMS of prolactin, a pituitary hormone exhibiting strong homology to GH. We suggested that prolactin may act via stimulating the production of a precursor of acetylcholine in the cholinergic neurons of the brain stem that have a fundamental role in the generation of REMS (32). In fact, prolactin secretion is chronically enhanced and prolactin (and GH) receptors are upregulated in mice overexpressing GH (3). Therefore, a contribution of prolactin to the promotion of REMS cannot be excluded, and the possibility may also be considered that GH stimulates REMS via prolactin receptors in the MT-rGH mice.

Rats with a defect in GHRH receptor signaling respond to a 4-h SD with less intense SWA during NREMS than do normal rats (30). The MT-rGH mice did not display alterations in the recovery sleep after SD. The enhancements in SWA during NREMS, however, either saturate after 4–6 h of SD (18), or further increments in SWA after longer SD are blunted because of the progressive increase in the number of short NREMS periods intruding into wakefulness during deprivation and because SWA may also appear during wake epochs during long SD (14). Therefore, the 12-h SD used in our experiments might have been too long to pick up slight differences in the sleep responses between the normal and the MT-rGH mice.

Increases in spontaneous NREMS time in the MT-rGH mice on the baseline day are difficult to explain in terms of our current understanding of the role of the somatotropic axis in sleep regulation. Several lines of evidence suggest that GHRH has a fundamental role in promoting NREMS (22). Production of GHRH is, however, suppressed and somatostatin is stimulated as a result of the negative feedback mediated by the high concentrations of circulating GH and IGF-1 in transgenic mice producing excess GH (3).

The experiments with octreotide suggest that signs of GHRH deficiency could be demonstrated in sleep regulation in the MT-rGH mice. The prompt inhibition of NREMS by octreotide and the enhancements in SWA during NREMS starting in hour 2 postinjection in normal mice correspond to the sleep responses to octreotide previously reported in rats (4). Enhancements in SWA occur at a time when surges of GH secretions also reoccur after octreotide (4). The immediate inhibition of sleep results in part from a behavioral activation mediated by octreotide-induced release of angiotensin in the hypothalamus, which elicits drinking, grooming, feeding, vasopressin secretion, and rises in blood pressure (15). These actions of octreotide can be blocked by means of an angiotensin-convertase inhibitor or by angiotensin receptor antagonists without interfering with the sleep responses (4). Hence, an inhibition of GHRH release by octreotide is assumed to be a major component of sleep suppression, whereas the late increases in SWA are attributed to the releases of the accumulated GHRH when the octreotide effects dissipate. The time courses of these actions correspond to the breakdown of octreotide with a half-life between 45 and 120 min (39). The SWA response was almost completely suppressed and the initial inhibition of NREMS was significantly attenuated in the MT-rGH mice, suggesting a decreased activity of GHRH. Despite this, spontaneous NREMS was slightly enhanced in these mice.

Previous studies on the effects of GH on sleep do not provide many clues for an understanding of the alterations in NREMS in the MT-rGH mice. Promotion of NREMS is not reported after acute administration of GH, and NREMS may in fact decrease due to the feedback inhibition of GHRH (25). Slight decreases in NREMS time and significant decreases in SWA during NREMS follow an acute withdrawal of GH in the rat (29). The time spent in NREMS is permanently decreased in rats with chronic GH deficiencies (30), and a role of GH cannot be excluded in those changes. Perhaps the observations most relevant to our results are from studies of sleep in patients with tumors secreting excess GH (2). In contrast to our findings, however, duration of NREMS is shortened in these patients. The EEG energy, including SWA during NREMS, is greatly enhanced, and this alteration disappears after the removal of the GH-producing adenoma. At variance with this, the EEG and SWA were normal in the MT-rGH mice. It is possible that IGF-1 contributes to the stimulation of NREMS because small doses of IGF-1 slightly increase NREMS in the rat (33). Nevertheless, unlike the promotion of REMS, stimulation of NREMS might not be a direct intracerebral action of GH. The reason for this assumption is that production of GH in the brain cannot block decreases in NREMS in transgenic mice deficient in GHRH and pituitary GH secretion (54).

Bartke et al. (3) suggest that some alterations in mice producing excess GH may be specific to chronic overstimulation of GH receptors and may not occur at acute or near physiological doses of GH. These features include various endocrine abnormalities and alterations in tissue metabolism. For example, secretions of
prolactin, ACTH, and corticosterone are permanently increased in mice overexpressing GH although GH does not normally stimulate these hormones. Chronic hyperprolactinemic rats also display slight increases in the time spent in NREMS, but an acute administration of prolactin does not promote NREMS (32). In transgenic mice with excess GH, concentrations of insulin in the plasma increase significantly, most likely because of a GH-induced insulin resistance. In contrast to acromegalic humans, however, the MT-rGH mice do not develop diabetes mellitus; the concentrations of plasma glucose are normal (3, 21). A major indication for the possible importance of metabolic alterations in sleep abnormalities is that the MT-rGH mice prefer higher than normal sugar intake, and behavioral sleep time normalizes when these mice are allowed to consume sucrose at will (42). GH and IGF-1 stimulate the immune system (reviewed in Ref. 17). Both hormones enhance basal and endotoxin-induced production of proinflammatory cytokines in macrophages (12, 40) and in thymic stromal cells (51), and signs of increased responsiveness of the immune system have been reported in mice producing excess GH (8). It is not clear whether significantly enhanced cytokine release occurs in the MT-rGH mice. GH greatly enhances the production of free radicals (10, 11). Elevated reactive oxygen species particularly in the brain are implicated in the accelerated aging of the MT-rGH mice (41). It has been proposed that NREMS protects against free radical processes and thus contributes to neuronal detoxification; oxidized-reduced glutathione, a key antioxidant system, promotes sleep (19).

The major message from the current findings in the MT-rGH mice is that modulation of sleep by the somatotropic axis cannot be restricted to the role of GHRH. Other members of this endocrine system, including GH, somatostatin, and IGF-1, also influence sleep. The enhancements in REMS and NREMS in the MT-rGH mice are actions independent of GHRH most likely mediated by some metabolic effects of these hormones.

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