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Sleep Organization in Hypo- and Hyperthyroid Rats

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Abstract. The relationship between thyroid hormones and mammalian sleep organization was studied in control, hypothyroid (with and without replacement therapy) and thyroxine-injected adult male rats. The results show an increased number of awakenings during slow wave sleep (SWS) in hypothyroid animals, whereas total sleep time, levels of SWS, paradoxical sleep, and diurnal organization were unaffected by thyroid status. Our findings indicate that adequate levels of thyroid hormone are necessary to sustain extended periods of SWS in the adult rat while hyperthyroid animals show no disruption of sleep organization. A corollary finding is that daily sleep quotas are independent of whole body metabolic rates.

In addition to their crucial role in the developing mammalian central nervous systen (CNS), thyroid hormones are important for normal CNS function in the adult. Untreated chronic hypothyroidism in adult humans is manifested by a constellation of symptoms ranging from listlessness to overt psychosis [13] and hyperthyroidism by hyperexcitability and emotional instability [38]. Similar changes in brain function have been observed in adult animals (e.g. rats) in which hypothyroidism decreases and hyperthyroidism increases spontaneous motor activity [10] as well as gross brain excitability [26, 34, 35]. In some species, thyroid hormones are also involved in the maintenance of various states of cyclic behavior, from running activity to hibernation [16, 23, 29], and themselves undergo characteristic cyclic changes such as circadian rhythmicity [27]. That thyroid activity is implicated in the maintenance of specific characteristics of sleep organization is not surprising although systematic studies in support of this relationship are rare. In humans, sleep stages 3 and 4 and paradoxical sleep are markedly shortened or absent in hypothyroidism [20, 25, 39] but prolonged in hyperthyroidism (especially sleep stages 3 and 4). In animals, few studies are available covering 24-hour sleep patterns and, in thyroxine-injected rats observations for short sleep periods did not disclose significant changes [9]. Thus far, studies relating thyroid hormones to brain electrical activity, as manifested by spontaneous [2, 5, 28] and evoked [15] responses, have been concerned with the characteristics of threshold, latency, waveform amplitude and frequency rather than with circadian variations as manifested in sleep/wake patterns.

In the present experiments, a systematic study of the effects of hypo- and hyperthyroidism on sleep pattern characteristics was achieved by 24-hour, continuous recordings of the electroencephalogram (EEG) and electromyogram (EMG). In particular, we were interested in investigating whether a relationship exists between daily sleep quotas and whole-body metabolism, and whether such a relationship could be altered by modifying the thyroid state.

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Materials and Methods

Animals, Care and Treatment

All experiments were conducted on male, Long-Evans rats, averaging 90 days of age on the day of sleep recording. The animals were initially housed 2 per cage and then individually, following implantation, to avoid gnawing of the implanted connector by cage-mates. All rats were maintained on a 12/12 h light/dark cycle (light: 8 a.m. to 8 p.m.; dark: 8 p.m. to 8 a.m.) at a room temperature of 23 °C. When approximately 50 days of age (body weight 210–240 g), the animals were divided into four groups of 8–9 animals each.

Group 1: Rats were surgically thyroidectomized under ether anesthesia.

Group 2: Rats were thyroidectomized as in group 1. Replacement therapy was initiated 21 days after thyroidectomy: it consisted of daily subcutaneous injections of thyroxine (*L*-thyroxine 10 μg/100 g body weight) [36] continuing for 25 days until the scheduled sleep recording date.

Group 3: Rats were sham operated to serve as controls for the thyroidectomized group. These animals were also injected on the same schedule as above with saline (0.9% NaCl, pH 8.0–8.5), the vehicle for *L*-thyroxine.

Group 4: Rats were given daily subcutaneous injections of *L*-thyroxine sodium, 0.4 mg/100 g body weight, for 17 days prior to sleep recording. The dosage and the duration of treatment have previously been found to produce hyperthyroidism [35].

All animals, except those in group 4, were transferred from standard rat chow (Purina) to a powdered low-iodine diet immediately following surgery. In the thyroidectomized animals (both untreated and receiving replacement therapy) the low-iodine diet was given in an attempt to inhibit growth of any residual thyroid tissue that may inadvertedly have been left following thyroidectomy or any supernumerary thyroid tissue. The controls received supplemental iodine as a 0.001% KI solution in drinking water. To insure proper calcium balance, parathyroidectomy being unavoidable with thyroidectomy, the thyroidectomized animals were given a 1% calcium gluconate drinking water solution.

Estimation of the thyroid state was by direct and indirect methods. The efficacy of thyroidectomy in inducing hypothyroidism was assessed by measuring T3 levels by radioimmunoassay (Antibodies Incorporated, Davis, Calif.) of blood taken at the end of the sleep recording period. Indirect measurements of the thyroid state included body weights and metabolic rates. Body weights were measured at 2-day intervals following surgery or onset of injections. Metabolic rates were determined 3 days prior to the sleep recording period by indirect calorimetry according to the method of *Grad* [14] in which oxygen consumption is measured by water displacement. The 15-min metabolic measurements were conducted between 9 and 10 a.m. with a constant temperature (28°C) within the metabolic chamber.

Electrode Implantation and Sleep Recording

Approximately 10 days prior to the scheduled sleep recording day, rats anesthetized with 60 mg/kg sodium pentobarbital, intraperitoneally, were implanted with electroencephalographic (EEG) and electromyographic (EMG) electrodes. Stainless steel roundhead screws (0–80 3/32) with presoldered 30-gauge copper wire leads, serving as EEG electrodes, were stereotaxically implanted in the skull over the frontal and occipital lobes. Flexible Teflon-coated silver wires were inserted into the nuchal musculature, serving as EMG electrodes. All electrode leads were connected to an amphenol plug which was cemented to the skull. Topical sulfathiazole was applied following surgery.

Sleep was evaluated in an electrically shielded wooden box, with one-way observation windows, located in a sound-attenuated, temperature-controlled recording room. The box was divided into two independent recording 'chambers' (each 46×46×31 cm) allowing dual recordings. Filtered and cooled air was supplied to the chambers, maintaining a constant temperture of 23 ± 1 °C. The light/dark cycle in the chamber was the same as in the animal colony.

For acclimation, animals were placed in the recording chambers 48 h prior to the onset of the recording period. After the 48-hour acclimation period, the rats were connected to a Grass polygraph (model 5D polygraph with a model 5E driver amplifier, and Grass 5P5D EEG and 5P3B EMG amplifiers); the leads were plugged into a slip ring connector (Air Flyte Electronics) in the recording chamber ceiling in order to allow free, unrestrained motion during the recording session. The sleep/wake activity of the animals was recorded over a 24-hour period and the electrical activity taped continuously for later analysis.

Sleep Scoring Procedure

Recorded EEG patterns were classified as slow wave sleep (SWS), paradoxical sleep (PS) and waking (A). SWS was identified by large amplitude, low frequency fronto-occipital (F-O) EEG activity accompanied by reduced EMG potentials (fig. 1A), while PS was identified by the low amplitude, high frequency activity of the F-O EEG in conjunction with low EMG potential (fig. 1B). The waking state was characterized by a high amplitude EMG accompanied by a low amplitude, high frequence F-O EEG (fig. 1C).

Each 1 min epoch of the polygraph record was scored as a period of PS, SWS or A. If two or more states occupied a single epoch, the epoch was scored according to the predominant state of the 1-min period.

The SWS and PS states were analyzed in terms of their frequency of occurrence, mean duration, and the total time occupied by the sleep states and expressed as a percentage of the total 24-hour recording period. In addition, diurnal variations were analyzed and the number and frequency of transitions were examined.

Statistics

Duncan's multiple range test was used to determine differences between the means of the measured sleep parameters in control and experimental animals.

Results

Direct and indirect measures of thyroid state indicate that thyroidectomy produced the hypothyroid state and supplemental thyroxine induced hyperthyroidism in unoperated animals or reversed the hypothyroid conditions in thyroidectomized animals. Serum T3 levels were significantly lower in thyroidectomized (0.15 ± 0.03 ng/ml) than in the sham-operated animals (0.47 ± 0.04 ng/ml). The persistent 30% T3 levels show that thyroidectomy and low iodine diet did not completely abolish thyroid hormone activity even though other indirect parameters were significantly affected, attesting to the severity of the thyroid condition. Serum T4 levels were not measured as two of the groups had been injected with thyroxine and such data would have provided no further information relative to the thyroid status of the animals.

Weight gain was reduced in both hypo- and hyperthyroid rats. On the day of sleep recording the body weights were: sham operated (controls) 280 ± 7 g; thyroidectomized

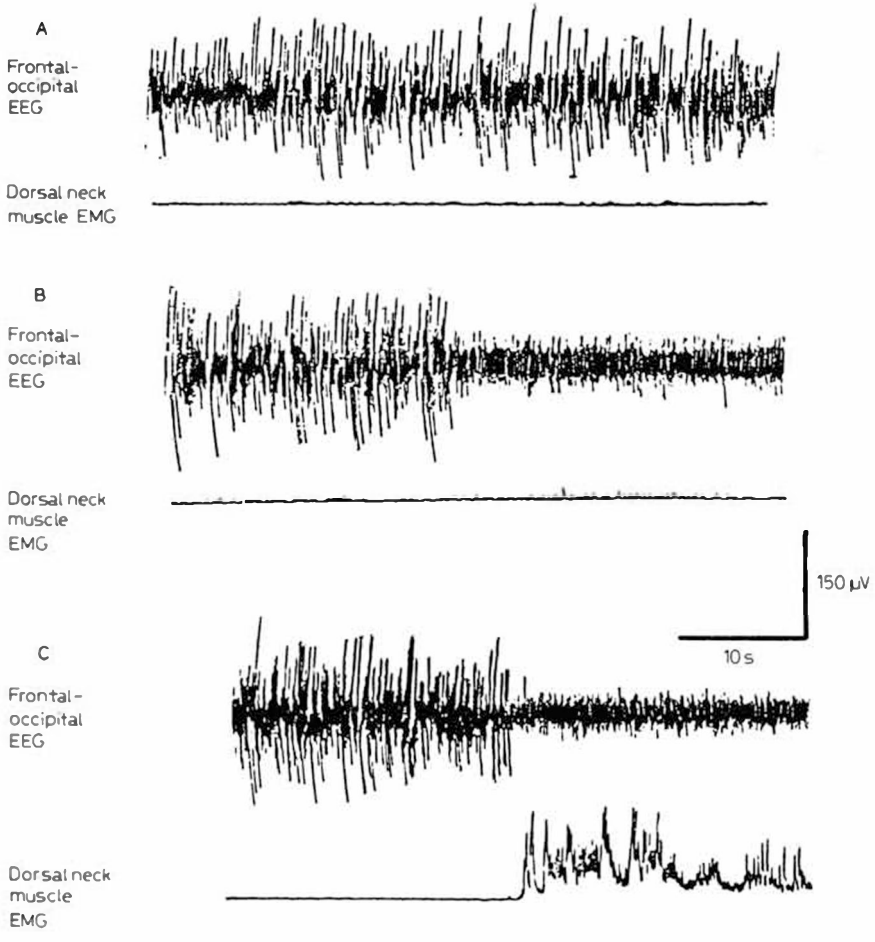

Fig. 1. Frontal-occipital EEG and integrated EMG in the rat during slow wave sleep (SWS), paradoxical sleep (PS) and the awake state. **A** SWS; identified by large amplitude, low frequency EEG activity accompanied by reduced EMG potentials. **B** Transition from SWS to PS; PS identified by a low amplitude, high frequency with low amplitude EMG. **C** Transition from SWS to awake state; waking characterized by a high amplitude EMG, accompanied by a low amplitude, big frequency EEG.

251 ± 4 g; thyroidectomized with T4 replacement 282 ± 9 g; and hyperthyroid 265 ± 5 g. The lower weight of the thyroxine-injected intact animals together with increased metabolic rate is a common manifestation of hyperthyroidism in rats. Oxygen consumption was 50% lower in thyroidectomized and 40% higher in the hyperthyroid than in the controls and normal in the thyroidectomized rats receiving replacement therapy.

The dimensions of sleeping characteristics including total time, frequency, duration, transitions and diurnal variations in control (euthyroid) rats are comparable to those described by other investigators [30]. In general, none of these characteristics is altered in hyperthyroid rats or in thyroidectomized animals receiving replacement therapy; however, untreated thyroidectomized rats are unable to sustain SWS episodes of normal duration.

Over the total 24-hour observation period, the proportions of total SWS time (48%), total PS time (12%) and total sleep time (the sum of SWS plus PS, 60%) do not show statistically significant differences among euthyroid, hyperthyroid and hypothyroid rats, but the number of SWS periods is significantly increased in the hypothyroid (106.5) compared to the control animals (82.5). The number of SWS periods is inversely related to their duration in the hypothyroid animals (table I).

Transitions (awake to slow wave, slow wave to paradoxical sleep, etc.) expressed as a percent of the total number of transitions in a 24-hour period (excluding the transition from awake to PS, which was 0 in all groups) indicate that the hypothyroid animals exhibit an increase in the number of transitions from SWS to the waking state (table II). The high number of SWS to waking transitions in the hypothyroid animals explains both the increase in the absolute number of SWS episodes and the decrease in the length of episodes in the presence of an unchanged total SWS sleep time.

Despite shortening of the SWS periods, the overall pattern of sleep/wakening cycles is unaltered in thyroidectomized animals. The 24-hour distribution of SWS in 2 representative rats, 1 thyroidectomized and 1 sham operated, is displayed in figure 2. Both recordings show the expected distribution of less SWS during the dark portion of the cycle compared to the light portion.

Table I. Sleep characteristics in euthyroid and hypothyroid or hyperthyroid rats (24 h): mean ± SE

Sleep characteristics	Experimental parameter	Groups			
		Sham (8)	Tx (9)	Tx + T4 (8)	T4 (8)
Sleep times during 24-hour observation (expressed as % of 24 record)	SWS, %	46.1 ± 3.39	47.8 ± 3.23	51.1 ± 3.22	45.4 ± 3.14
	PS, %	10.3 ± 0.99	11.8 ± 0.97	9.9 ± 1.06	12.4 ± 1.10
	TST, %	56.4 ± 3.75	59.7 ± 3.83	61.5 ± 4.49	58.9 ± 3.92
Frequency of sleep state occurrence during 24-hour observation	SWS, n	79.4 ± 5.19	106.5 ± 6.10*	82.5 ± 5.34	83.2 ± 4.95
	PS, n	62.1 ± 4.77	58.5 ± 3.47	57.4 ± 4.24	56.9 ± 4.17
	TSP, n	58.0 ± 2.97	80.9 ± 3.80*	61.9 + 2.54	62.8 ± 2.93
Mean durations of sleep states	SWS, min	8.1 ± 0.42	6.5 ± 0.60*	8.5 ± 0.42	8.7 ± 0.67
	PS, min	3.0 ± 0.76	3.2 ± 0.47	2.7 ± 0.64	3.5 ± 0.42
	SE, min	13.5 ± 1.34	10.5 ± 1.02*	14.1 ± 1.10	14.8 ± 0.71

SWS = Slow wave sleep; PS = paradoxical sleep; TST = total sleep; TSP = total daily sleep period; SE = sleep episodes;
Sham = sham operated, euthyroid-control; Tx = thyroidectomized animals, hypothyroid; Tx + T4 = thyroidectomized animals receiving T4 replacement, euthyroid; T4 = thyroxine injected, hyperthyroid. Numbers in parentheses indicate number of animals per group.
* $p \leq 0.05$ when compared with sham operated (control).

Table II. Sleep state transitions in euthyroid, hypothyroid or hyperthyroid rats (24 h)

Transitions	Groups			
	Sham (8)	Tx (9)	Tx + T4 (8)	T4 (8)
A-SWS	58.0 ± 2.97[1]	80.9 ± 3.80*	61.9 ± 2.54	62.0 ± 2.93
SWS-PS	62.1 ± 4.77	58.5 ± 3.47	57.4 ± 4.24	56.9 ± 4.17
SWS-A	26.3 ± 3.32	48.0 ± 2.83*	25.1 ± 2.97	27.8 ± 3.50
PS-A	38.7 ± 2.93	32.9 ± 2.97	36.7 ± 3.18	33.7 ± 3.36
PS-SWS	22.4 ± 2.54	25.6 ± 2.40	20.6 ± 2.33	21.6 ± 2.72
A-PS	0	0	0	0
Total	244.9 ± 16.5	201.8 ± 13.81	206.4 ± 12.7	199.5 ± 11.0

Sham = Sham operated, euthyroid - control; Tx = thyroidectomized animals, hypothyroid; Tx + T4 = thyroidectomized animals receiving T4 replacement, euthyroid; T4 = thyroxine injected, hyperthyroid; A = awake; SWS = slow wave sleep; PS = paradoxical sleep. Numbers in parentheses indicate number of animals per group.
[1] Mean ± standard error for number of transitions.
* $p \leq 0.05$ when compared with sham operated control.

Discussion

The effect of thyroidectomy in shortening the length but increasing the number of SWS episodes adds support to the view that thyroid hormones play a role in regulating some aspects of brain function in the adult. This role, however, seems to be limited to maintenance of normal sleep by normal thyroid hormone levels, demonstrated by SWS alterations in hypothyroidism and restoration of normal SWS pattern after replacement therapy in the hypothyroid rats. In contrast, thyroxine excess does not alter any of the sleep characteristics measured, an observation in agreement with other studies in which thyroxine injections failed to alter rat sleep patterns [9]. Our results also indicate that neither the circadian distribution of sleep nor the total amount of SWS or PS states are significantly affected by the thyroid state.

The high frequency of SWS awakenings in the hypothyroid state may, perhaps, be related to the low metabolic state of the animal. The length of sleep episodes has been shown to be shortened in several conditions generally associated with energy depletion, such as food deprivation in animals [1, 3, 8] and either fasting or weight reduction in hu-

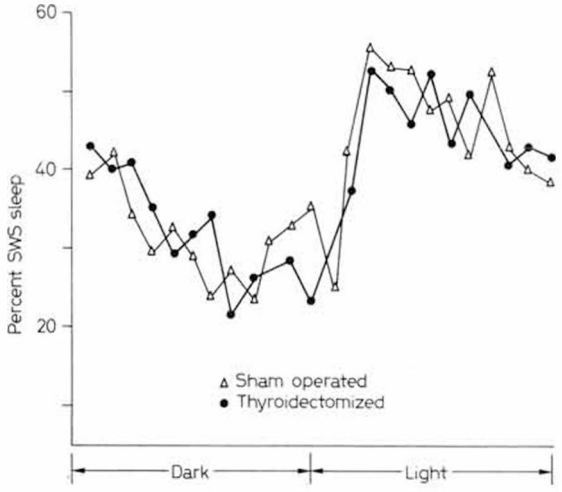

Fig. 2. Representative diurnal rhythms of SWS sleep for the euthyroid and hypothyroid rat. Each symbol indicates the % SWS within a 1-hour period for a sham-operated '△' and thyroidectomized '0' animal.

mans [6, 7, 21]. One postulated function of sleep is the regulation of energy expenditures by 'enforcing rest and limiting metabolic requirements...' [40]. It may be possible, therefore, to associate sleep alterations with reduced metabolic rate [37] as occurs in both hypothyroidism and undernutrition. However, the restriction of alterations to a single sleep characteristic in hypothyroidism (despite a significantly reduced metabolic rate) and the lack of any alteration in hyperthyroidism (despite a significantly increased metabolic rate) suggest that, within individual organisms, sleep organization is not involved in regulation of energy requirements in response to changes in metabolic rate.

Whether or not thyroid hormones affect the metabolic rate of cerebral tissue remains controversial; early studies suggest that the regulatory action of the hormones is operative only in the developing brain [12] and more recent studies either challenge the earlier findings [31] or ascribe other metabolic regulatory roles to the hormones in the adult brain [17, 32, 34]. Among these latter roles, of interest in relation to sleep, is the action exerted by thyroid hormones on brain neurotransmission, in particular serotonergic neurotransmission frequently implicated in sleep function [19, 24]. It has been reported in the rat that the serotonin (5-HT) levels are significantly lower in the hypothyroid than euthyroid cerebral hemisphere, a region normally containing high numbers of 5-HT synaptic endings, and in the mesodiencephalon, a region containing the serotonergic cell bodies [17]. Thus, the significant increase in the number of awakenings from SWS in hypothyroid rats may be attributed to disrupted serotonin metabolism or distribution in the brain of the hypothyroid animal.

Another possible explanation for the influence of the hypothyroid state on sleep involves the hypothalamic thyrotropin-releasing hormone (TRH). An increased CNS sensitivity to TRH has been reported in hypothyroid rats [4]. TRH, present throughout the CNS and described as a putative neurotransmitter, has been ascribed numerous actions ranging from evoking responses in individual cerebral neurons to initiating complex behavior patterns. Pharmacologic doses of TRH in humans cause prolonged wakefulness, accompanied by decreased amounts of stage 2 and paradoxical sleep [22]. It remains to be established whether TRH plays a true direct physiological role in sleep pattern organization or whether it acts through its effects on thyroid function.

The thyroid state can alter the levels of certain other hormones (growth hormone, corticosterone) which affect sleep. In rats, thyroidectomy abolishes daily variations in plasma levels of growth hormone but does not alter its baseline level [33] and in humans, the pharmacological blockade of the peaks of growth hormone does not modify sleep [11] implying that the effects of altered thyroid hormone levels on sleep are not mediated through growth hormone. Although thyroidectomy can alter corticosterone levels [33], complete adrenalectomy in rats only alters the circadian distribution of paradoxical sleep, but not sleep pattern organization [18]. All of these data imply a direct action of thyroid hormones on sleep rather than through their effects on other hormone levels.

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