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Thyroid and Thyroxine Effects on Adrenoreceptors in Relation to Circadian Activity

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VESSOTSKIE, J. M., P. McGONIGLE, R. C. MOLTHEN AND D. L. McEACHRON. *Thyroid and thyroxine effects on adrenoreceptors in relation to circadian activity.* PHARMACOL BIOCHEM BEHAV **46**(1) 251-257, 1993.—Experiments were conducted to ascertain if changes in central adrenergic receptors could be associated with altered circadian activity patterns induced by thyroparathyroidecomy (TPX) and thyroxine. An initial experiment used TPX and sham-operated rats that had been exposed to dim red light for 7 months. The α and β receptor densities were compared in the suprachiasmatic nuclei (SCN), preoptic (PO), septum, and caudate-putamen. TPX animals showed significant reductions in β_1 and β_2 receptor densities in SCN and PO, and α_1 densities in SCN, but no other changes. A second experiment, lasting 4 months, examined the effects of thyroxine, which has been shown to reverse the period-shortening effects of TPX surgery. Thyroxine significantly increased β_1 receptors in both the SCN and ventromedial hypothalamus (VMH), the only regions that displayed significant reductions in TPXs during the second experiment. Increases of sevenfold and threefold were observed in the SCNs of TPXs and shams, respectively, but thyroxine's action in the VMH was limited to TPX animals, an effect that mimics thyroxine's action on circadian activity rhythms.

Thyroid Rat Circadian Adrenergic Thyroxine Catecholamine Suprachiasmatic SCN Ventromedial hypothalamus VMH Neuroreceptor Caudate-putamen Preoptic Septum Thyroparathyroidectomy Autoradiography

SEVERAL endocrine hormones or systems are known to modify overt circadian rhythmicity. In rats, both thyroid state and estrogen level influence the expression of activity rhythms. Thyroparathyroidectomized (TPX) male rats have been observed to display shorter circadian periods in wheel-running activity, more consolidated activity patterns, and increased levels of activity (21,22). The same results are reported for ovariectomized (OVX) rodents supplied with estrogens (13,27). The observation that TPX and intact female rats did not differ from each other or from TPX males on circadian activity parameters while remaining significantly different from intact males (22) suggested that thyroid state and estrogen effects were nonadditive (12). Hence, these two factors may act through a common mechanism.

One such mechanism may involve adrenergic neurotransmission. Adrenoreceptors, and most especially β receptor concentrations, appear to be influenced by hypothyroidism and estradiol in a similar manner. Hypothyroidism decreases β-adrenergic receptor density in the cerebral cortex (7,23) and the hypothalamus (1), while estradiol treatment also decreases β-adrenergic receptor density in the cerebral cortex (16,24). Both hypothyroidism and estrogens decrease α receptors as well, but these data involve different subtypes. Thus, estradiol treatment decreases α_1 adrenoreceptor concentrations in the medial preoptic, SCN, pineal, median eminence, and the ventral medial hypothalamus, whereas hypothyroidism decreases α_2 receptors in both the brain and heart (1,23). Potentially, the similar effects of hypothyroidism and estrogens on circadian behavior and β receptor densities could be functionally related.

There are additional reasons to suspect adrenergic involvement in circadian rhythms aside from the linkage between estrogens and hypothyroidism. Affective disorders have been associated with alterations in the period, phase, and amplitude of circadian rhythms (8), and chronic administration of antidepressants has been reported to lengthen free-running periods (28). One effect of most antidepressants is to increase the extracellular concentration of norepinephrine (NE), which could result, over time, in adaptive changes in adrenergic receptor function. Also, Rosenwasser (19,20) showed that clonidine, an α_2 agonist, shortened the free-running circadian period in constant light while reducing the amplitude and the overall activity level. These effects were reversed after the termination of clonidine treatment. These results support the

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hypothesis that some causal relationship exists between modifications in circadian rhythms and adrenergic systems.

The objective of these experiments was to determine if a relationship exists between thyroid hormone levels and adrenergic receptor densities in the areas of the brain associated with circadian rhythms. The purpose was to establish a link between the behavioral changes being observed and alterations in receptor concentrations. This is a difficult undertaking given that the behavioral changes are being expressed as a statistical shortening in activity period and heightened activity levels rather than the presence or absence of some easily quantifiable stereotyped behavior. To gain some confidence that the changes in receptor densities, if observed, could be functionally related to the behavior, the rats were examined under two different experimental conditions. In the initial experiment, TPX and sham-operated rats were exposed to constant dim red light of varying intensity over a period 7 months. In the second experiment, animals were exposed to dim red light of a single intensity for 4 months, but during the second 2 months, one-half of the animals were given chronic thyroxine treatment. Three criteria for linking receptor changes with behavioral changes were used: 1) any changes must be consistent across the two experiments; 2) any changes associated with TPX surgery must be reversed by T4 treatment; and 3) any changes must correlate with alterations observed in circadian activity rhythms.

METHOD

Subjects

Sprague–Dawley male rats were used in these experiments. They were thyroparathyroidectomized (TPX) at 55 days of age and received at 60 days. Each animals was housed in a separate cage that recorded the revolutions of the running wheel using an on-line computer. The accommodations were temperature controlled, and the intensity and duration of exposure to light was regulated. The animals were fed laboratory rat chow and water supplemented with calcium lactate (2% by weight) ad lib.

In the first experiment, eight animals (four TPX, four sham) were kept in dim red light that varied in intensity from 0.5 to 2.0 lux for 7 months. At the end of this time, the animals were sacrificed and used for α- and β-adrenergic receptor analysis. These animals formed part of an experiment that was being conducted to determine the effects of red light intensity on TPX and sham rats' circadian activity rhythms.

In the second experiment, 18 animals (10 TPX, 8 sham) were maintained on a 12L : 12D cycle (lights on at 6 a.m. EST) for approximately 1 month. After entrainment was achieved, the animals were exposed to constant dim red light (<1 lux) for the rest of the experiment. The animals were allowed to free-run for 7 weeks, to establish a baseline free-running rhythm. After this period, the animals were injected SC with either T4-containing or blank capsules (Vivo-Trial, Endocon, Walpole, MA). The animals were removed from their cages and anesthetized with methoxyflurane (Metofane, Pittman-Moore, NJ). The injections were performed in the dark room under dim red light conditions. Five TPX and four sham animals received T4 capsules and five TPX and five shams received blanks. The animals were returned to their cages in the cabinets and were kept in constant conditions for 8 weeks. After the period of free-running activity following the injections, the animals were sacrificed. T3 and T4 levels and α and β adrenoreceptor densities were measured in all animals.

Tissue Preparation

The animals were sacrificed by carbon dioxide inhalation. Approximately 5 cc of blood was then obtained from each animal by cardiac puncture for T4 and T3 analysis. The blood was centrifuged for 20 min at 5000 rpm and the serum was frozen at -40°C until analysis. The animals were decapitated and their brains were removed and stored at -70°C until the time of sectioning.

Fifty consecutive 20-μ thick sections from each brain were cut using a cryostat and thaw mounted onto gelatin-coated microscope slides. The sampled area was the part of the hypothalamus that corresponds to pages 20–27 of the Pelligrino, Pelligrino, and Cushman stereotaxis atlas (15). The slides were desiccated under vacuum for 3–7 h and stored at -70°C until they were used.

Quantitative Autoradiography

The β-adrenergic receptor assay followed the procedures established by Rainbow and coworkers (18). Frozen sections were thawed, dried, and then incubated at 23°C for 60 min in 20 mM Tris-HCl with 0.9% NaCl, pH 7.4, and 200 pM [^{125}I]pindolol, a nonselective β-adrenergic antagonist. Selective β-adrenergic antagonists were added so that receptor subtypes could be measured. To visualize β_1 receptors, a selective β_2 antagonist, ICI 118,551, at a concentration of 50 nM, was added. Addition of 70 nM ICI 89,406, a selective β_1 antagonist, allowed for measurement of β_2 adrenoreceptors. Nonspecific binding was measured in the presence of 100 μm L ($-$)-isoproterenol, a nonselective β-adrenergic agonist. After incubation, the sections underwent three 20-min washes in Tris-saline buffer solution at 4°C, were rinsed in ice-cold water, and dried on a slide warmer. The slides were arranged in X-ray cassettes and apposed to Hyperfilm-3H from Amersham for 72 h. Kodak GBX developer/replenisher and fixer were used to develop the film. The software package BRAIN (Drexel University) was used to perform a quantitative analysis of the autoradiography.

The α_1 adrenoreceptor assay was based on previously established protocols (17,25). Sections were incubated for 30 min at 23°C in 170 mM Tris-HCl, pH 7.4, and 2 nM [^{3}H]prazosin, a highly selective α_1 antagonist. To measure nonspecific binding, 10 μM phentolamine-HCl, a nonselective α-adrenergic antagonist, was added. Following the incubation, the sections were washed twice in buffer solution at 4°C for 10 min each. Finally, the sections were rinsed in ice-cold distilled water, dried on a slide warmer, and apposed to film for 60 days.

To visualize α_2 receptors, the procedures were based upon published methods (2,14,29). Sections were incubated for 60 min in a solution containing the buffer, 50 mM Tris-HCl, pH 7.7, and 2 nM [^{3}H]PAC (para-aminoclonidine), an α_2 agonist. Phentolamine-HCl (10 μM) was used to define nonspecific binding. The sections were then washed in ice-cold buffer for 5 min, then 10 min, and finally dipped in distilled water and dried. These sections were apposed to film for 6 weeks. The films of both α receptor subtypes were developed and analyzed following the same procedure as the β receptor subtypes.

In the initial experiment, the regions chosen for analysis were the suprachiasmatic nuclei (SCN) and preoptic areas (medial preoptic) (PO), which are known to be involved in circadian rhythms and sleep; and the caudate-putamen (CPu) and lateral septum (Sep) at level 20 (15), which served as a kind of internal control. If thyroid state exerted a global effect on adrenergic receptors, it would not be possible to establish any

specific linkage between changes in thyroid status and behavioral alterations. Measurements of CPu and Sep were included to check for potential global changes. In the second experiment, the ventromedial hypothalamus (VMH) was added to the list because of potential involvement with secondary oscillating (food restriction-sensitive pacemakers) systems in the rat.

Statistical Analysis

Results from the initial experiment were analyzed by analysis of variance (ANOVA). When significant results were found between TPX and sham animals in the first comparison, those regions and receptor subtypes were compared in TPXs and shams treated with blank pellets by *t*-test (one-tailed) in the second experiment. The effects of the T4 treatment and interactions with surgery were examined by two-way ANOVA. Where significant heterogeneity of variances were uncovered, data were converted into base 10 logarithms prior to analysis. Scheffe's test was used for post hoc comparisons.

RESULTS

Experiment 1

The results of the first experiment are shown in Table 1. The β_1-, β_2-, and α_1-adrenergic receptors in the SCN were significantly decreased in TPX animals. Figure 1 shows the effects of surgery on β receptors in the SCN. The levels of β_1 and β_2 subtypes were also decreased in the PO of TPX animals, and the Sep of TPX rats showed lower levels of β_1 adrenoreceptors. The β_1 subtype did not have altered levels in the CPu, indicating that the changes observed were region specific. Other regions that were not influenced by the TPX state include the β_2 subtype in the Sep and CPu, the α_1 subtype in the PO, Sep, and CPu, and the α_2 subtype in any examined region (Table 1).

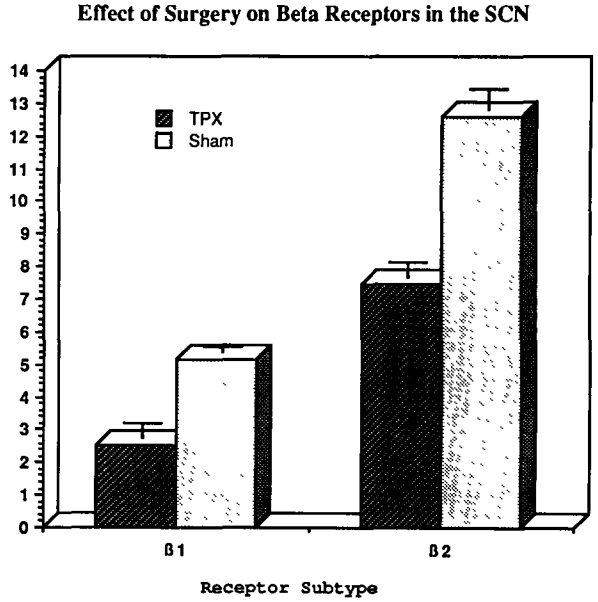

FIG. 1. Effects of thyroparathyroidectomy (TPX) on β receptor densities in the suprachiasmatic nuclei (SCN). Error bars indicate the SE.

Period estimates for each rat were obtained by blind raters. Raters drew lines on computer-generated actograms to provide the estimates. A one-way ANOVA with repeated measures (measuring the effects of different light intensities) indicated that TPX rats' periods were significantly shorter than

TABLE 1

RADIOACTIVE CONTENT (μg/dl) OF SELECTED BRAIN REGIONS COMPARING THYROPARATHYROIDECTOMIZED (TPX) AND SHAM (INTACT) RATS FOR ADRENERGIC RECEPTOR CONTENT

		TPX			SHAM		
		n	$\bar{X}$	SE	*n*	$\bar{X}$	SE
ALPHA-1	CPU	4	10.50	0.19	4	11.26	0.54
	SEP	4	17.06	1.78	4	16.13	0.65
	SCN	4	20.07	0.30	3	22.47	0.35
	PO	4	25.71	0.61	4	28.35	0.90
ALPHA-2	CPU	4	9.87	0.47	4	8.67	0.07
	SEP	4	33.57	0.63	4	36.60	0.66
	SCN	3	22.96	0.37	4	24.75	1.80
	PO	4	32.56	0.89	4	31.05	2.01
BETA-1	CPU	4	30.07	0.71	4	27.99	0.41
	SEP	4	11.29	0.47	4	14.94	0.28
	SCN	2	2.55	0.32	2	5.16	0.11
	PO	4	4.20	0.10	2	6.94	0.10
BETA-2	CPU	4	17.34	0.47	4	19.46	0.05
	SEP	4	5.68	0.27	4	6.12	0.25
	SCN	2	7.64	0.29	2	12.62	0.40
	PO	3	4.32	0.20	2	7.41	0.28

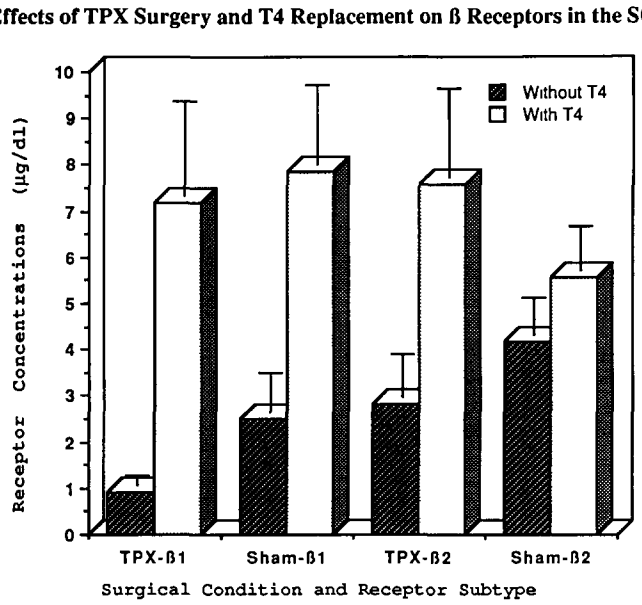

FIG. 2. Effects of thyroparathyroidectomy (TPX) and thyroxine (T4) treatment on β receptor densities in the suprachiasmatic nuclei (SCN). Error bars indicate the SE.

shams for the overall experiment [average difference was 0.21 h, $F(1, 13) = 4.83, p < 0.05$].

Experiment 2

Of the regions showing significant reductions in adrenergic receptor densities in Experiment 1, only the β_1 concentrations of the SCN were significantly lowered when comparing TPX and sham rats injected with blanks in Experiment 2 ($t = 2.185$, $p < 0.05$). All other previously measured areas were not significantly different in either β or α receptor concentrations. In the VMH, a Scheffe test revealed a significant reduction in β_1 receptor densities ($F = 6.23$, $p < 0.05$). Since the VMH had not been measured in the first experiment, only the β_1 receptor densities in the SCN showed a consistent influence of the TPX surgery.

Thyroxine (T4) treatment significantly increased β_1 receptor densities in the SCN of both TPX and sham-operated rats,

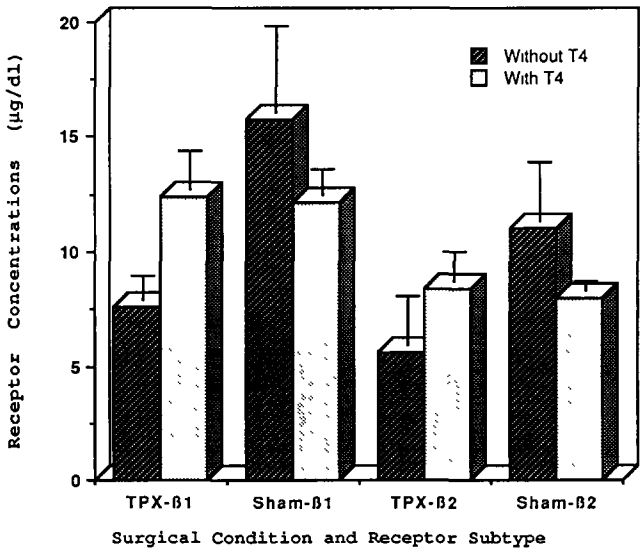

FIG. 3. Effects of thyroparathyroidectomy (TPX) and thyroxine (T4) treatment on beta receptor densities in the ventromedial hypothalamus (VMH). Error bars indicate the SE.

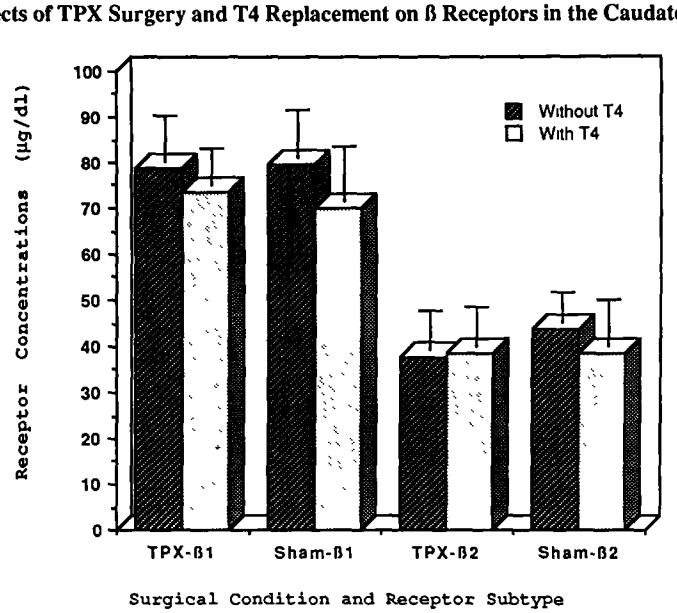

FIG. 4. Effects of thyroparathyroidectomy (TPX) and thyroxine (T4) treatment on beta receptor densities in the caudate-putamen. Error bars indicate the SE.

$F(1, 13) = 19.89$, $p < 0.01$. The increase was sevenfold for TPX and threefold for shams, but the interaction was not significant, $F(1, 13) = 0.88$, NS, indicating that T4 had a similar effect on both groups of animals. The β_2 receptor concentrations were also increased in both groups, $F(1, 12) = 6.14$, $p < 0.05$, albeit to a lesser degree. These data are graphed in Fig. 2.

When examining the effect of T4 on β_1 receptors in the VMH, a nearly significant interaction effect was noticed, $F(1, 13) = 4.29$, $p < 0.06$. A Scheffe test revealed that T4 treat-

TABLE 2

RADIOACTIVE CONTENT (µg/dl) OF BRAIN REGIONS FOR THYROPARATHYROIDECOMIZED (TPX) AND SHAM RATS COMPARING THE EFFECTS OF THYROXINE (T4) REPLACEMENT ON ADRENERGIC RECEPTOR DENSITIES

		TPX			SHAM			TPX + T4			SHAM + T4		
		n	$\bar{X}$	SE	*n*	$\bar{X}$	SE	*n*	$\bar{X}$	SE	*n*	$\bar{X}$	SE
ALPHA-1	CPU	5	8.06	0.37	4	6.53	1.20	4	6.09	0.93	4	6.27	0.58
	SEP	4	12.39	0.88	4	10.25	1.69	4	10.84	1.21	4	12.51	0.69
	SCN	4	21.29	0.73	4	19.83	0.74	4	20.45	1.91	4	21.65	0.68
	PO	5	26.79	1.89	4	24.56	1.00	4	23.94	2.25	4	23.11	1.61
	VMH	4	27.83	0.79	4	28.51	2.03	4	29.43	1.65	4	30.21	2.08
ALPHA-2	CPU	5	1.79	0.37	4	2.16	0.41	4	2.13	0.36	4	1.99	0.28
	SEP	5	23.87	1.74	4	29.07	2.02	4	28.13	1.53	4	27.86	2.94
	SCN	5	21.87	2.69	4	22.93	0.98	4	25.31	3.03	4	26.22	1.94
	PO	5	22.85	2.54	4	23.56	0.55	4	22.26	1.13	4	19.07	1.48
	VMH	5	21.96	0.96	4	20.19	2.03	4	22.72	0.89	4	19.99	0.84
BETA-1	CPU	5	78.89	10.08	4	79.78	10.05	4	73.59	7.87	4	70.06	11.89
	SEP	4	26.77	4.61	4	21.28	6.19	4	23.26	5.69	4	24.49	4.74
	SCN	5	0.92	0.19	4	2.49	0.85	4	7.20	2.02	4	7.86	1.71
	PO	5	8.37	4.08	4	11.30	3.39	4	9.90	2.85	4	9.51	2.05
	VMH	5	7.62	1.05	4	15.78	3.76	4	12.38	1.68	4	12.12	1.13
BETA-2	CPU	5	37.47	8.48	4	43.44	6.69	4	38.41	8.54	4	38.47	10.07
	SEP	4	3.66	1.65	4	4.05	1.05	4	3.88	0.67	4	4.27	1.52
	SCN	5	2.83	0.91	4	4.17	0.79	4	7.57	1.93	4	5.56	0.96
	PO	5	5.40	1.32	4	6.10	1.84	4	4.90	1.26	4	5.91	2.14
	VMH	4	5.61	2.18	4	11.02	2.65	4	8.44	1.25	4	7.99	0.40

ment had resulted in a significant increase in β_1 receptor densities in the VMH of TPXs ($F = 6.30$, $p < 0.05$), which was not observed in T4-treated sham animals. These data are shown in Fig. 3.

For all other regions and receptor subtypes examined, neither TPX surgery nor T4 treatment exerted any significant effects. Figure 4 shows a representative result from the CPu. The results are summarized in Table 2.

DISCUSSION

Hypothyroid male rats show a shorter circadian activity period and higher activity levels compared to intact animals (10,21,22). These behavioral effects can be reversed using thyroxine (T4) (10). These experiments demonstrated a region-specific decrease in β_1-adrenergic receptor densities in the SCN and VMH of thyroparathyroidectomized rats, an effect that can also be reversed using T4. Together, these results support the hypothesis that thyroid state may affect activity rhythms and levels through alterations in central adrenoreceptors.

In the first experiment, β_1, β_2, and α_1 receptor densities in the SCN (a master circadian pacemaker) were all decreased in the TPX rats as compared to intact animals. Lower β_1 and β_2 receptor densities were also observed in preoptic areas, and the septum had lower levels of β_1 adrenoreceptors. Only the decreased density of β_1 receptors in the SCN could be replicated in the second experiment. There are several possible explanations for this inconsistency. The animals used in the initial experiment were exposed to red light for a longer period and were several months older at the time of sacrifice when compared with the males used in the second study. Either circumstance might be causally related to the results. It is potentially significant in this regard that experiments in this laboratory have shown that certain differences between shams and TPXs in activity rhythms appear to increase as the animals age (11). Specifically, older rats show a decrease in activity rhythm consolidation that is not observed in TPX animals. The changes in receptor densities may reflect this change in behavior. In addition, the light intensity was systematically varied in the first experiment, and this has been shown to alter the pattern of TPX rats' activity rhythms as well as the free-running periods of both sham and TPX rats (unpublished observations; Schull, personal communication). However, it is also true that the number of animals used in the first experiment was quite small and this may have resulted in false positive results. Only the decrease in β_1 receptor density in the SCN demonstrated both consistency from the first to the second study and was reversible with T4 treatment. Clearly, thyroid state helps to determine the extent of adrenergic stimulation received by this important circadian oscillator.

However important this finding, the pattern of β_1 receptor density increase with T4 treatment does not mirror the circadian activity changes associated with T4 treatment. Sham animals show a significant increase in β_1 receptor density, but were not observed to lengthen their circadian activity periods, as did the TPX rats (10). The only receptor subtype and region where changes did appear to correlate with the circadian behavior were β_1 receptors found in the VMH. TPX animals have fewer β_1 receptors in the VMH, an effect that is reversed with T4 treatment. Sham animals, however, show no changes in β_1 receptor densities associated with chronic T4 exposure. Unfortunately, the VMH was not examined in the first experiment so that consistency cannot be demonstrated. However, T4's ability to selectively reverse the loss of receptors associated with TPX surgery is tightly suggestive. The VMH is a nucleus associated both with feeding and with entrainment to food restriction cycles (4,9). In adult rats, a surgically lesioned VMH results in a rise of food intake and a fall in sympathetic activity (4). Thus, the VMH may represent a focal point for thyroid influences on feeding and activity rhythms.

The idea that thyroid hormones regulate neural adrenergic receptors was suggested in the early 1980's in association with affective disorders by Whybrow and Prange (26). They suggested that an affective state may be altered by transmission in the central noradrenergic pathways. The association between thyroid abnormalities and affective disorders (3,6) may be explained, in part, based upon the influence of thyroid hormone on β-adrenergic receptors that mediates this adaptation. In this experiment, excess thyroid hormone altered β-adrenergic receptor densities in TPX and sham-operated animals so the levels converged on a set point, the significance of which is not understood at this time. These results support the theory that thyroid hormone, by acting at the β-adrenergic receptors, provides an adaptive mechanism.

Technical advances have permitted a closer examination of genetic regulation of hormonal signals. The β_2-adrenoreceptor gene has been cloned and the expression of this gene has been shown to be regulated by glucocorticoids at the level of transcription (5). Furthermore, the thyroid hormone receptor is a member of the steroid receptor gene family. Since genes known to be under the control of thyroid hormone, such as growth hormone, α-myosin, and thyrotropin, have been reported to display both transcriptional and posttranscriptional regulation, direct effects on adrenergic gene expression may be expected.

In conclusion, these experiments have demonstrated that in rats thyroid hormone levels alter adrenoreceptor density, most especially the β_1 subtype, in a region-specific manner. Of the two regions where the most significant changes were found, the SCN is definitely and the VMH is probably involved in regulating the expression of circadian rhythms. Combined with other data, such as Rosenwasser's clonidine studies, these results support the hypothesis that adrenergic activity may modify the rat circadian system. Further experimentation is needed to confirm this hypothesis, determine the extent of the modification, and discover the relationship, if any, between these results and affective disorders.

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