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Behavioral and Autonomic Thermoregulation in the Rat Following Propylthiouracil-induced Hypothyroidism[1]

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GORDON, C. J. *Behavioral and autonomic thermoregulation in the rat following propylthiouracil-induced hypothyroidism.* PHARMACOL BIOCHEM BEHAV **58**(1) 231–236, 1997.—A reduced body temperature is a common symptom of hypothyroidism and may result from a deficiency in metabolic heat production. However, a reduced metabolism does not necessarily imply a failure in thermoregulatory control if other thermoeffectors, in particular behavioral thermoregulation, are operative. To address this issue, selected ambient temperature (T_a) in a temperature gradient, core temperature (T_c), heart rate (HR), and motor activity (MA) were monitored via radiotelemetry in euthyroid rats and rats made hypothyroid by the administration of 0.05 mg/ml propylthiouracil (PTU) in drinking water for approximately 15 days. Core temperature of PTU-treated rats was reduced by 0.3°, whereas selected T_a was increased by 2.3°. PTU treatment led to significant reductions in HR, whereas MA was unaffected. Thermoregulatory behavior did not reverse the PTU-induced hypothermia, suggesting that PTU-induced hypothyroidism leads to a regulated reduction in body temperature (i.e., decrease in the set point). A reduced set point seems to be an adaptive response that lowers the metabolic requirements for thermoregulation in the hypothyroid rat. © 1997 Elsevier Science Inc.

Heart rate Core temperature Temperature gradient Motor activity Propylthiouracil Serum T_3 Serum T_4

HYPOTHERMIA is one of many pathologic sequelae that may occur in hypothyroid experimental animals and humans (12,13,19). The secretion of thyroxine (T_4) from the thyroid gland is of paramount importance to the maintenance of a normal basal metabolic rate. T_4 and the conversion to the active hormone triiodothyronine (T_3) is critical in the modulation of activity of enzymes, which contribute to basal metabolic processes such as Na-KATPase and others (8,14).

The reduced metabolism in hypothyroidism is considered to be the primary explanation for the hypothermia. However, with a reduced metabolic rate, one would still assume that the function of thermoreceptors, both peripheral and internal, and the efficacy of behavioral thermoregulation would remain operative in hypothyroidism. This assumption is questionable in view of the preponderance of hypothermia in hypothyroidism. An experimental model to quantify behavioral thermoregulatory responses during hypothyroidism is essential to unravel the reasons behind hypothyroid-induced hypothermia. For example, a hypothyroid animal allowed to thermoregulate behaviorally could select warm ambient temperatures (T_a) to reverse the hypothermia. Conversely, if an environment is selected where a hypothyroid animal is still hypothermic, then the central neural control of body temperature should be altered.

A temperature gradient to measure behavioral thermoregulatory responses combined with radiotelemetry to monitor core temperature is an excellent means to assess the thermoregulatory responses of hypothyroidism in unstressed rats. Propylthiouracil (PTU) is an antithyroidal agent that inhibits the production of T_4 outside of the central nervous system

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(11) and lowers body temperature in rats when administered in the diet (1,19). PTU can be administered in the drinking water, acts quickly, and is cleared from the circulation in a matter of a few hours. The purpose of this study is to assess the relationship between behavioral and autonomic thermoregulatory responses in the rat made hypothyroid by the administration of PTU.

MATERIALS AND METHODS

Fischer 344, 60-day-old male rats were obtained from Charles River Laboratories. The animals were maintained in cages lined with wood shavings at a T_a of 22°, relative humidity of 50%, and a 12:12 light:dark photoperiod.

The animals were implanted with a radiotransmitter (Data Sciences Inc., St. Paul, MN) to monitor heart rate, core temperature, and motor activity (5). Briefly, rats were anesthetized with sodium pentobarbital (50 mg/kg; i.p.). An incision approximately 2 cm long was made along the midline of the skin and abdominal muscles. The electrocardiogram leads of the transmitter (model CTA-F40) were tunneled under the skin and positioned around the thorax. The body of the transmitter was placed inside the abdominal cavity and held in place with a suture to the abdominal muscles. The muscles were sutured with 4-0 silk and the skin closed with wound clips. The rat was given 30,000 units of penicillin (i.m.) and allowed to recover for at least 1 week before experimentation. Rats were studied at an age of approximately 3 months. The temperature calibration of the transmitter was verified after removal from each rat.

The temperature gradient has been explained in detail elsewhere (3). The system allows the monitoring of selected T_a, motor activity, and the telemetry variables (core temperature, heart rate, and motor activity) simultaneously in single rats permitted free movement within a T_a range of approximately 10–37°. Food and water were provided ad libitum in the middle of the gradient. Air was directed into the top of the gradient at four equally spaced locations at a flow rate of approximately 2.5 L/min. Air flow was shielded from blowing directly on the animal in the gradient. The runway of the temperature gradient was illuminated with miniature lamps positioned at 10-cm intervals.

Approximately 7 days after surgery, the animals were allowed to continue drinking tap water or were given PTU (6-n-propyl-2-thiouracil; Sigma, St. Louis, MO). The PTU solution was prepared once or twice a week by dissolving approximately 100 mg PTU in 1 L of water, which was slowly heated and stirred until the PTU dissolved. The volume of the stock solu-

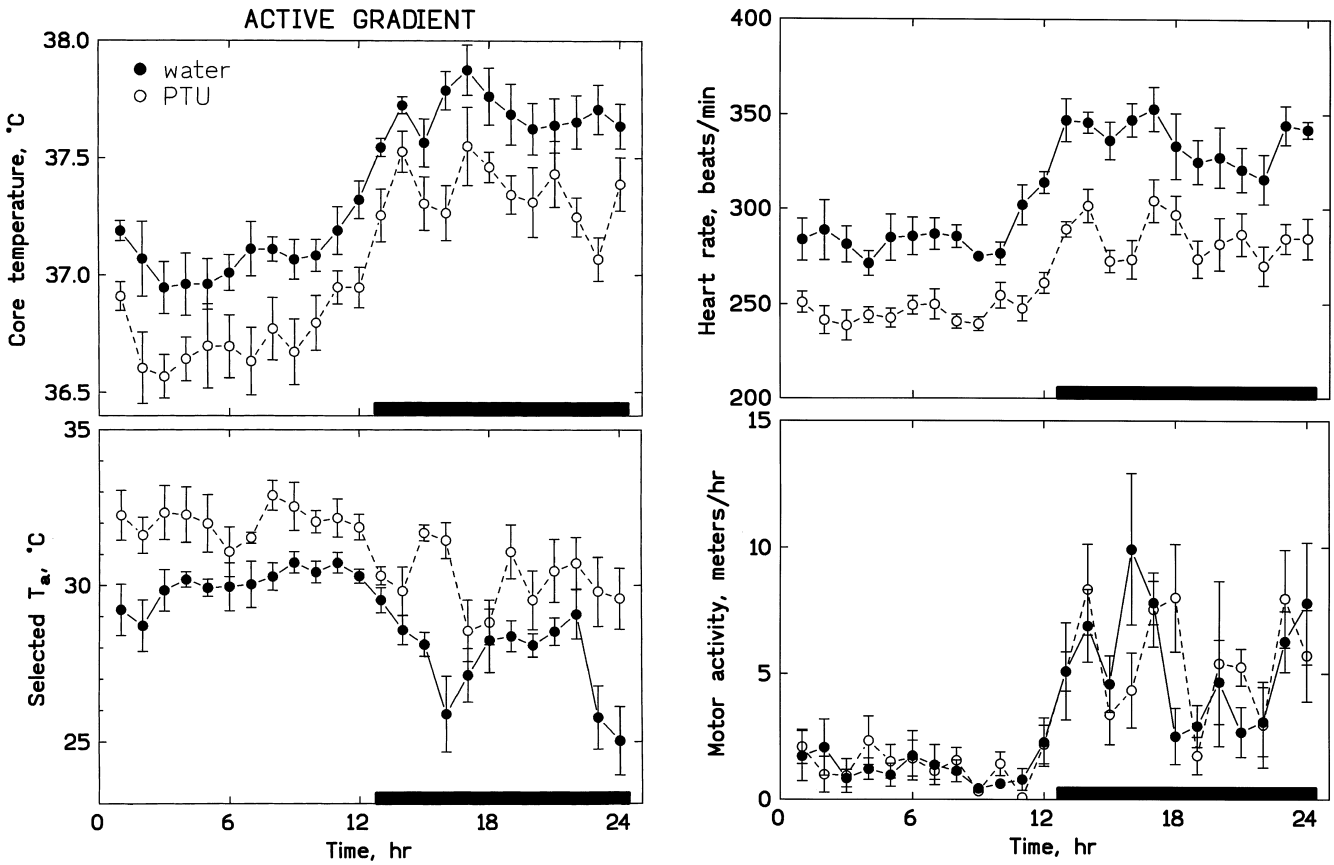

FIG. 1. Effect of PTU treatment on core temperature, selected T_a, heart rate, and motor activity of F344 rats maintained in a temperature gradient. $n = 6$ for both groups except for heart rate of the PTU group in which $n = 5$. Bar indicates period of darkness. Repeated measures ANOVA: core temperature [treatment, $F(1,10) = 32.8$, $p = 0.0002$; time, $F(23,230) = 19.7$, $p < 0.0001$; interaction, NS], selected T_a [treatment, $F(1,10) = 36.3$, $p = 0.0001$; time, $F(23,230) = 7.2$, $p < 0.0001$; interaction, $F(23,230) = 2.8$, $p = 0.044$], heart rate [treatment, $F(1,10) = 12.6$, $p = 0.005$; time, $F(23,230) = 10.6$, $p < 0.0001$; interaction, NS], and motor activity [treatment, (NS); time, $F(23,230) = 7.8$, $p < 0.0001$; interaction, (NS)]. NS = not significant.

TABLE 1

MEAN ± SE OF CORE TEMPERATURE (T_C), SELECTED AMBIENT TEMPERATURE (T_a), HEART RATE (HR), AND MOTOR ACTIVITY (MA) AVERAGED OVER THE LIGHT PHASE, DARK PHASE, AND 24 HR PERIOD IN F344 RATS MAINTAINED IN OPERATIVE AND ISOTHERMAL GRADIENTS.

		Period of Analysis		
Treatment	Variable	Light	Dark	24 h
		Active Gradient		
Water	T_C	37.08 ± 0.04	37.68 ± 0.04	37.38 ± 0.04
PTU	T_C	36.74 ± 0.05	37.34 ± 0.07	37.04 ± 0.04
		(0.0005)	(0.002)	(0.0002)
Water	T_a	30.0 ± 0.3	27.7 ± 0.2	28.8 ± 0.2
PTU	T_a	32.0 ± 0.5	30.1 ± 0.3	31.1 ± 0.3
		(0.004)	(0.0001)	(0.0001)
Water	HR	287 ± 6	335 ± 7	311 ± 5
PTU	HR	247 ± 4	285 ± 6	266 ± 5
		(0.01)	(0.001)	(0.005)
Water	MA	1.3 ± 0.2	5.4 ± 0.5	3.3 ± 0.3
PTU	MA	1.4 ± 0.2	5.5 ± 0.6	3.4 ± 0.4
		(NS)	(NS)	(NS)
		Inactive Gradient		
Water	T_C	37.19 ± 0.06	37.65 ± 0.02	37.42 ± 0.04
PTU	T_C	36.89 ± 0.06	37.38 ± 0.07	37.14 ± 0.06
		(0.006)	(0.007)	(0.003)
Water	T_a	22.6 ± 0.3	21.5 ± 0.2	22.0 ± 0.2
PTU	T_a	22.7 ± 0.4	21.7 ± 0.2	22.2 ± 0.3
		(NS)	(NS)	(NS)
Water	HR	347 ± 2	379 ± 8	363 ± 5
PTU	HR	327 ± 4	350 ± 6	339 ± 5
		(0.002)	(0.008)	(0.004)
Water	MA	1.1 ± 0.2	5.3 ± 0.8	3.2 ± 0.4
PTU	MA	1.3 ± 0.3	5.5 ± 1.1	3.4 ± 0.7
		(NS)	(NS)	(NS)

Numbers in parentheses indicate statistical significance for water vs. PTU treatments. NS = not significant.

tion was raised to bring the concentration of PTU to 0.05 mg/ml. A cross-over design was utilized whereby the animals were treated with water or PTU; after testing in the gradient, the treatment schedules were reversed. Animals formerly given PTU were given water for at least 2 weeks before retesting. The amount of PTU consummed was estimated from the change in weight of the drinking water bottle at approximately weekly intervals; however, this method could not take into account the PTU lost from spillage. The duration of PTU treatment in individual animals was 16–25 days. The estimated dose of PTU per rat was 21.0 mg, and the daily estimated dosage was 4.6 mg PTU/(kg/day).

The PTU treatment used in the present study was expected to cause marked reductions in serum levels of T_3 and T_4. For example, rats administered 0.1% PTU in their drinking water exhibit a 58% reduction in T_3 and 79% reduction in T_4 (15). Nonetheless, the effectiveness of the PTU treatment in this study to lower serum levels of T_3 and T_4 was assessed in another set of rats without telemetry implants. Male F344 rats were administered PTU in their drinking water (n = 3), and another set of animals (n = 3) served as controls. After 14 days of treatment, a blood sample was taken by clipping the end of the tail and allowing approximately 1.0 ml of blood to drip into a collecting tube. The blood was allowed to clot, and the serum was separated and frozen for later analysis. A cross-over design was instituted as in the same procedure used earlier; i.e., the control rats were administered PTU and the PTU rats were administered water for 14 days. After this time, the blood sampling procedure was repeated. T_3 and T_4 were measured with solid-phase radioimmune assay by using antibody-coated tubes (Diagnostic Products Corp., Los Angeles, CA).

Experiments were designed to evaluate the effects of PTU on the regulation of core temperature when the temperature gradient was active and inactive. A rat was first placed in the temperature gradient for 60 h. The water and PTU treatments were continued when the animals were in the gradient. At the end of 60 h, the temperature gradient was inactivated and rendered isothermal to a T_a of 22° by circulating water at a temperature of 18–20°C through both ends of the system and through coils of Tygon tubing wrapped around the copper housing of the gradient. Mean T_a within the inactive gradient decreased by approximately 1.0°C from day to night due to fluctuations in the room environmental control. The rat was left in the gradient for an additional 48 h of testing at the isothermal temperature while the telemetry variables were monitored.

Telemetry and selected T_a data were collected at 1.0-min intervals and averaged into 1.0-h bins for statistical analysis. Repeated measures analysis of variance (ANOVA) was used to assess the effects of PTU treatment and time in the gradient on each of the variables. The 1-h data points were also averaged into mean responses for the light phase, dark phase, and 24-h periods in the gradient. This analysis was limited to the final 24 h of treatment in the active and inactive temperature gradients. Significant differences in mean light, dark, and 24-h responses were analyzed for significance by using Student's *t*-test.

RESULTS

Active Gradient

PTU treatment caused a significant reduction in core temperature and heart rate and an elevation in selected T_a but had no effect on motor activity (Fig. 1). Core temperature of the PTU group remained below control levels throughout the light and dark phases. Control and PTU groups displayed the typical nocturnal elevation in core temperature at the onset of the dark phase. Overall, PTU caused a 0.29°C reduction in the 24-h mean core temperature (Table 1). There was no significant interaction between treatment and time, suggesting that PTU caused a consistent lowering of core temperature over the 24-h period in the gradient.

Selected T_a of the PTU group was significantly warmer than that of the control group (Fig. 1). Selected T_a during the light phase was 30°C and 32°C in control and PTU groups, respectively (Table 1). There appeared to be distinct differences in the time course of selected T_a as indicated by the significant treatment by time interaction. At the start of the dark phase, selected T_a of the control group decreased over a 4-h period to 26°C, whereas selected T_a of the PTU group decreased slightly at the start of the dark phase but then exhibited an upward return to light phase levels. There was also a marked difference in selected T_a at the end of the dark phase, with the control group selecting T_as approximately 5°C cooler than PTU animals.

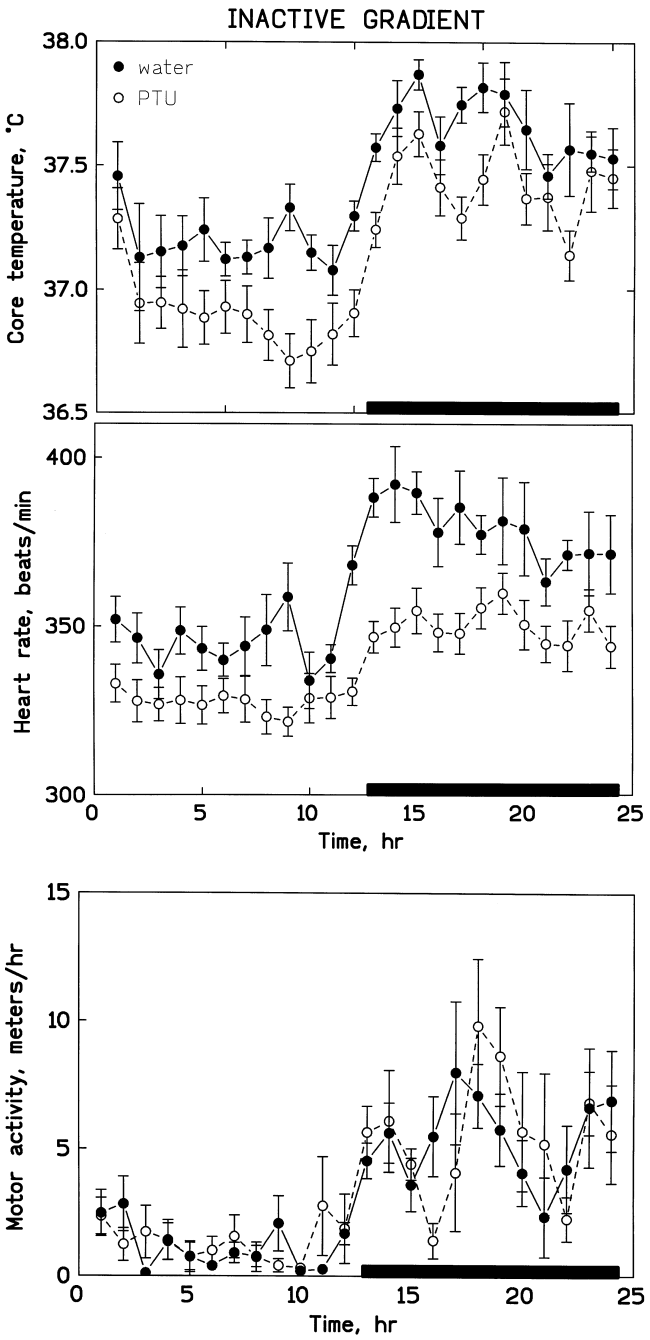

FIG. 2. Effect of PTU treatment on core temperature, selected T_a, heart rate, and motor activity of F344 rats maintained in an isothermal gradient (T_a = 22°C). Repeated measures ANOVA: core temperature [treatment, $F(1,12) = 16$, $p = 0.0018$; time, $F(23,276) = 11.1$, $p < 0.0001$; interaction, NS], heart rate [treatment, $F(1,12) = 14.8$, $p = 0.0023$; time, $F(23,276) = 16.3$, $p < 0.0001$; interaction, $F(23,276) = 2.1$, $p = 0.0034$], and motor activity [treatment, NS; time, $F(23,230) = 7.4$, $p < 0.0001$; interaction, NS]. Abbreviations and sample sizes as in Fig. 1.

Overall, selected T_a during the dark phase was reduced by approximately 2°C in the control and PTU groups (Table 1).

PTU treatment resulted in an approximate 50 beats/min decrease in heart rate. Both control and PTU groups exhibited a clear nocturnal elevation in heart rate during the dark phase in the gradient. Motor activity in the temperature gradient also showed a distinct nocturnal elevation in both groups; however, PTU treatment had no effect on motor activity.

Inactive Gradient

The core temperature of control and PTU rats in the inactive gradient was similar to that of the active gradient (Fig. 2). The core temperature of the PTU group was significantly below that of the controls, and there was no difference in core temperature with the gradient, active or inactive. Housing animals in the inactive gradient led to a significant increase in heart rate in both the control and PTU groups; however, heart rate of the PTU group was still significantly below that of the controls over the 24-h period [PTU treatment, $F(1,12) = 21.3$, $p = 0.0006$; gradient, $F(1,12) = 73.6$, $p < 0.0001$]. Compared with the active temperature gradient, heart rate of control and PTU groups in the inactive gradient was elevated by 52 and 73 beats/min, respectively (Table 1). Motor activity was similar between the control and PTU groups in both the active and inactive gradients.

Serum T_3 and T_4

PTU treatment led to marked reductions in serum T_3 and T_4 (Fig. 3). When averaging the first treatment group and the cross-over group together, T_3 and T_4 were reduced by 82% and 99%, respectively, following 14 days of PTU treatment ($p < 0.0001$). The group of rats that were first exposed to PTU had a serum T_4 level of 41.4 ng/ml by the end of the 14-day water treatment. This level is similar to the serum T_4 level of the rats that were first placed on water for 14 days (40.0 ng/ml), suggesting that the 14-day cross-over treatment allowed sufficient time for recovery of T_4 production. However, serum T_3 differed significantly between the first control group (0.707 ng/ml) and the cross-over control group (0.464 mg/ml; $p = 0.01$).

DISCUSSION

When housed in an active temperature gradient permitting behavioral thermoregulatory responses, animals administered PTU selected warmer T_as than controls but maintained a reduced core temperature similar to PTU-treated animals housed at 22°C (i.e., inactive gradient). Rats in an active gradient had the option of selecting T_as as warm as 37°C. The PTU-treated rats did not select such warm T_as, which undoubtedly would have reversed the hypothermic effects of PTU. Exposure to a T_a of 34°C is sufficient to reverse the hypothermic effects of PTU in the rat (Yang and Gordon, unpublished observations). Hence, the set point for control of body temperature seems to be reduced in PTU-induced hypothyroidism because the thermoregulatory behavior of the rat does not fully correct for the hypothermic effects of PTU.

The PTU treatment design used in the present study appeared to be effective in inducing hypothyroidism, as shown by the 82% and 99% reductions in serum T_3 and T_4, respectively. Thermogenesis in brown adipose tissue (7) and other tissues and organs (14) depends on the presence of T_4. The reduced heart rate in the animals administered PTU appears to reflect a hypothyroid-mediated suppression in metabolic rate. Interestingly, motor activity was not altered by PTU, suggesting that the hypothermia cannot be attributed to a deficit in themogenesis derived from motor activity.

There is a general consensus that reduced body temperature in hypothyroid animals is attributed to deficits in thermo-

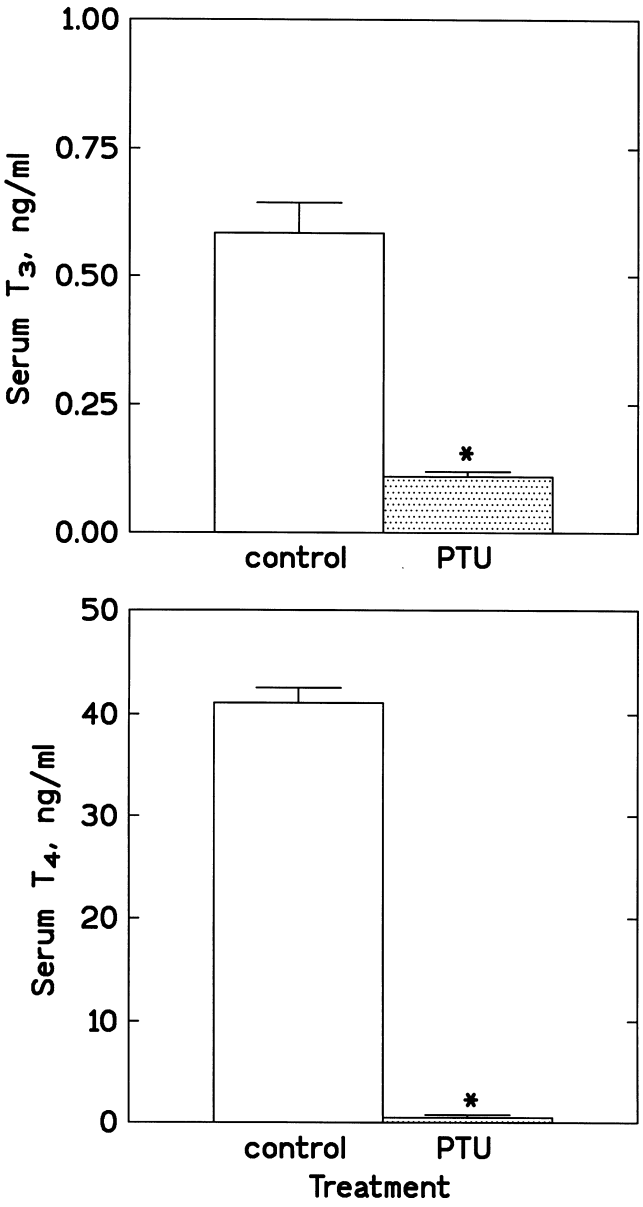

FIG. 3. Serum T_3 and T_4 levels in the F344 rat following treatment with water (control) or PTU (0.05 mg/ml) for 14 days. Data plotted are the mean ± SE of the first treatment and cross-over treatments. $n = 6$ per treatment group. *Significant difference between control and PTU groups (unpaired t-test, $p < 0.0001$).

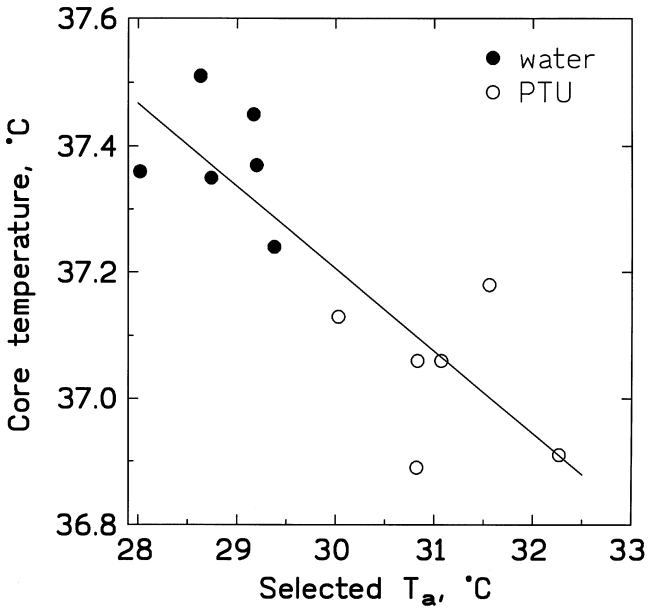

FIG. 4. Relationship between selected T_a and core temperature averaged over a 24-h period in rats ($n = 12$) treated with water and PTU. Linear regression analysis: $Y = 41.1 - 0.13 * X$, $r^2 = 0.715$, $p = 0.0005$, slope = 0.

genesis (2,4,9). However, the behavioral thermoregulatory observations in the present study indicate that the hypothermia seen in hypothyroidism involves altered function of the central nervous system. That is, with a normal thermoregulatory response to hypothermia, an increase in the selected T_a of the hypothyroid animal would be expected. Although, a 2.3°C rise in the 24-h selected T_a was seen in the PTU-treated rats, this behavioral response was insufficient to overcome the hypothermic effect of PTU. Using an operant behavioral thermoregulatory system, cold-exposed thyroidectomized rats worked for radiant heat reinforcements much faster than did controls (9,20). Although core temperature was not measured in these operant studies, the thyroidectomized rats were assumed to hypothermic. The combined use of telemetry and behavioral regulation in a temperature gradient in the present study demonstrates that hypothyroid rats prefer warmer environments while remaining hypothermic.

Rats treated with PTU have the capability to raise core temperature to normal levels via activation of autonomic thermoeffectors, which was evident from the circadian rhythm of core temperature in hypothyroid rats in the active and inactive gradients. Bauer et al. (1) also observed a circadian temperature rhythm in rats treated with PTU (0.02%) and sodium ipodate (0.1% in drinking water) for 4 weeks, along with approximately a 0.7°C reduction in mean core temperature. Because selected T_a is reduced at night, normal rats seem to rely primarily on autonomic thermoeffectors to raise core temperature at night (5). The same principle holds for hypothyroid rats; however, the abrupt rise in selected T_a of PTU animals 2 h after the start of the dark phase suggests that behavioral thermoregulation facilitates the nocturnal elevation in core temperature.

The abundance of data on the incidence of hypothermia in hypothyroid humans (13), a condition that is potentiated in the aged (10), suggests the possibility of an alteration in the central control of body temperature. That is, humans and other mammals normally regulate their core temperature with behavioral thermoregulatory responses rather than with autonomic responses, which have substantial metabolic requirements. Hypothyroidism leads to a myriad of neurochemical alterations that could be responsible for a reduction in the central neural control of body temperature. For example, surgically induced hypothyroidism causes alterations in activity of brain neurotransmitter systems (6,12,18). Thyroidectomy accentuates the hypothermic effects of the carbachol, a cholinergic agonist (12). Such neurochemical alterations resulting from hypothyroidism exemplify potential mechanisms for inducing a reduction in set point in the rat treated with PTU.

There was an inverse relationship between the 24-h mean of selected T_a and core temperature in control and PTU-treated rats (Fig. 4). Analysis of the slope of the regression analysis indicates that the ratio of Δ selected T_a to Δ core temperature is 7.6:1. This relationship is consistent with current theories of thermoregulatory control, and this ratio represents the relative differences in thermal sensitivity between the thermoreceptors in the core and skin of the rat. For example, by using a surgically implanted thermode to clamp body temperature at specific levels, Sakurada et al. (16) determined the effect of T_a on the threshold hypothalamic temperature (T_h) for activation of thermoeffector mechanisms in the rat. The ratios of ΔT_a to ΔT_h were between 5:1 and 8:1, depending on the thermoeffector. These ratios are comparable to the ratio of selected T_a:core temperature of the euthyroid and hypothyroid rats. Overall, the relationship shown in Fig. 4 illustrates that as core temperature is reduced from PTU, there is a linear increase in preference for warmer T_as, a behavioral response that essentially balances the activity of central and peripheral thermoreceptors.

To summarize, fine changes in core temperature of the hypothyroid rat can be quantified with radiotelemetry. The differences were more evident in the animal adapted to a temperature gradient for at least 24 h, thereby reducing the effects of stress from a novel environment on thermoregulation (3,17). The 24-h mean core temperature difference of control and PTU-treated rats was only 0.3°C, a relatively small difference that nonetheless has a marked impact on behavioral thermoregulation. The data suggest that the set point for body temperature is reduced in the PTU-treated rat. This behavioral and autonomic response to regulate body temperature at a lower level may indeed be an adaptive response. That is, with PTU-induced hypothyroidism, autonomic thermoregulatory effectors may be insufficient to maintain a normal body temperature. Regulating core temperature at a lower level may be adaptive because the requirements placed on thermoregulatory effectors are reduced.

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REFERENCES

1. Bauer, M. S.; Soloway, A. Dratman, M. B.; Kreider, M.: Effects of hypothyroidism on rat circadian activity and temperature rhythms and their response to light. Biol. Psychiatry 32:411–425; 1992.
2. Fregly, M. J.; Cook, K. M.; Otis, A. B.: Effect of hypothyroidism on tolerance of rats to heat. Am. J. Physiol. 204:1039–1044; 1963.
3. Gordon, C. J.; Lee, K. A.; Chen, A.; Killough, P.; Ali, J. S.: Dynamics of behavioral thermoregulation in the rat. Am. J. Physiol. 261:R705–R711; 1991.
4. Gordon, C. J.: Temperature regulation in laboratory rodents. New York: Cambridge University Press; 1993.
5. Gordon, C. J.: 24-Hour control of body temperature in rats. I. Integration of behavioral and autonomic effectors. Am. J. Physiol. 267:R71–R77; 1994.
6. Henley, W. N.; Chen, X.; Klettner, C.; Bellush, L. L.; Notestine, M. A.: Hypothyroidism increases serotonin turnover and sympathetic activity in the adult rat. Can. J. Physiol. Pharmacol. 69:205–210; 1991.
7. Himms-Hagen, J.: Brown adipose tissue thermogenesis: role in thermoregulation, energy regulation and obesity. In: Schonbaum, E.; Lomax, P., eds. Thermoregulation: physiology and biochemistry. New York: Pergamon Press; 1990:327–414.
8. Horwitz, B. A.: Neurohumoral regulation of nonshivering thermogenesis in mammals. In: Wang, L. C. H.; Hudson, J. W., eds. Strategies in cold, natural torpidity and thermogenesis. New York: Academic Press; 1978:619–653.
9. Laties, G.; Weiss, B.: Thyroid state and working for heat in the cold. Am. J. Physiol. 197:1028–1034; 1959.
10. Maclean, D.; Taig, D. R.; Emslie-Smith, D.: Achilles tendon reflex in accidental hypothermia and hypothermic myxoedema. Br. Med. J. 2:87–90; 1973.
11. Meyers, F. H.; Jawetz, E.; Goldfien, A.: Review of medical pharmacology. Los Altos: Lange Medical Publications; 1978.
12. Mori, M.; Akuzawa, M.; Yamaguchi, M.; Michimata, T.; Iriuchijima, T.; Kobayashi, S.: Hypothyroidism enhances carbachol-induced hypothermia in the rat. Res. Commun. Chem. Pathol. Pharmacol. 65:97–104; 1989.
13. Northover, B.; O'Malley, B. P.; Rosenthal, F. D.: Alterations in systolic time intervals in primary hypothyroidism as a consequence of warming. J. Clin. Endocrinol. Metab. 56:185–188; 1983.
14. Oppenheimer, J. H.: Thyroid hormone action at the cellular level. Science 203:971–979; 1979.
15. Rondeel, J. M. M.; de Greef, W. J.; Klootwijk, W.; Visser, T. J.: Effects of hypothyroidism on hypothalamic release of thyrotropin-releasing hormone in rats. Endocrinology 130:651–656; 1992.
16. Sakurada, S.; Shido, O.; Fujikake, K.; Nagasaka, T.: Relationship between body core and peripheral temperatures at the onset of thermoregulatory responses in rats. Jap. J. Physiol. 43:659–667; 1993.
17. Singer, R.; Harker, C. T.; Vander, A. J.; Kluger, M. J.: Hyperthermia induced by open-field stress is blocked by salicylate. Physiol. Behav. 36:1179–1182; 1986.
18. Singhal, R. L.; Rastogi, R. B.; Hrdina, P. D.: Minireview: brain biogenic amines and altered thyroid function. Life Sci. 17:1617–1626; 1975.
19. Thompson, E. B.; Lum, L.: A time-course study of hypothyroidism-induced hypotension: its relation to hypothermia. Arch. Int. Pharmacodyn. 283:141–152; 1986.
20. Weiss, B.; Laties, V. G.: Behavioral thermoregulation. Science 133:1338–1344; 1961.