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Activity and Catch-Up Growth in Hypothyroid Rats

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NIKOLETSEAS, M M. *Activity and catch-up growth in hypothyroid rats* PHARMAC. BIOCHEM. BEHAV 14(4) 443–446, 1981 —Hypothyroidism was induced in 38-day old male rats by feeding the animals a chow diet supplemented with propylthiouracil (PTU, 0.1% by weight) for 43 days Wheel activity of PTU animals was not significantly different from that of euthyroid, ad lib feeding controls but it was significantly lower when compared to pairfed controls Body weight was significantly lower than that of euthyroid ad lib controls. Active PTU rats weighed more than pairfed active, while nonactive PTU weighed less than pairfed nonactive controls After 75 days of PTU discontinuation catch-up growth of PTU animals was not complete· both body weight and tibia length were significantly lower in the PTU condition in comparison to euthyroid, ad lib feeding condition. However, no difference existed between the catch-up growth of PTU and pairfed animals It was suggested that growth arrest observed in early hypothyroidism may be partly due to factors nonspecific to thyroxine absence, such as hypophagia.

Hypothyroidism Feeding Food restriction Activity Skeletal growth

DESPITE the fact that the effects of thyroidectomy on wheel activity in rats were studied as early as 1927 [12], it is not clear how the absence of thyroxine influences this behavior. Hoskins [12] and Lee and Buskirk [13] reported no change in activity following thyroidectomy. However, Richter [19] criticised these early studies for not having produced histological evidence for absence of thyroid regeneration. In his 1933 study [19] Richter concluded that absence of thyroid tissue is related to a definite reduction in wheel activity. This conclusion received support by a later report [11] which was the first of these experiments to use statistics. With the advent of goitrogenic compounds inactivation or inhibition of synthesis of thyroid hormones could be effected without resorting to surgical operations; the latter, aside from the physical trauma, involved the removal of parathyroid tissue. Rats made hypothyroid by feeding a diet containing propylthiouracil (PTU) have been reported to maintain normal activity levels [9]. A more recent study also reported no change in the activity of thiouracil-fed rats maintained on a premixed diet, but a self-selecting hypothyroid group was found to be hypoactive [15].

The present experiment was primarily designed to provide further evidence on the effects of drug-induced hypothyroidism on wheel activity in the rat. The second aim of this study was to assess catch-up growth after discontinuation of the drug.

METHOD

Animals

Forty-eight male Sprague-Dawley rats (Madison, WI) were used. At the beginning of the experiment they were 38 days old (body weight 122.6 ± 6.6 g). Animals of this age were used so that the effects of hypothyroidism on skeletal growth could be assessed. It is known that rate of skeletal growth remains high till about 80 days of age [21].

Materials and Apparatus

Propylthiouracil was mixed in the diet (ground Purina chow) in the proportion of 0.1% by weight. The active animals were individually housed in Wahmann wheels (diameter 35.5 cm); and adjoining cage (26×15×13 cm) contained a spillproof metal food cup and a water tube (affixed on the outside). The nonactive animals were individually housed in Hoeltge cages (24 ×18×18 cm) in which food cups and water tubes were attached as described above. All groups received ground Purina chow.

Procedure

Six groups were formed, 8 animals/group. In four of these groups animals were randomly assigned thus making a

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TABLE 1
SUMMARY OF BEHAVIORAL AND AUTOPSY DATA
MEANS AND STANDARD ERRORS OF THE MEANS

	PTU		Euthyroid		Pairfed	
	Active	Nonactive	Active	Nonactive	Active	Nonactive
Activity*	2872 ±501		1888 ±312		8171 ±854	
Body weight (g)†						
Pretreatment	121 9 ±2 0	124.3 ±2.0	120 8 ±2 8	122.9 ±3.0	121 6 ±2 6	124 3 ±1 9
Treatment	183.4 ±6 1	180 6 ±3 1	310 0 ±8.2	316 1 ±9 4	160 7 ±7 8	201 4 ±7.4
Recovery	362 2 ±9 1	359 4 ±9 9	414 0 ±11 9	417.7 ±10 6	351 6 ±7.5	354 5 ±7 8
Tibia (cm)	4 11 ±0 02	4 11 ±0 01	4 32 ±0.02	4 30 ±0.03	4 12 ±0 01	4 15 ±0.04
Cumulative food intake (g)	544.4 ±18 4	563.6 ±16.2	895.5 ±13 2	899 0 ±18 7		

*Mean daily number of revolutions during the last 20 days of hypothyroid state
†Means of the last day of the phases indicated

2×2 factorial design (drug×activity): PTU-active, PTU-nonactive, euthyroid-active, euthyroid nonactive. Two additional groups were used as extra controls, mainly for the evaluation of skeletal growth of the hypothyroid animals, which are hypophagic. These extra controls were: pairfed to PTU-active, and pairfed to PTU-nonactive. The two groups were themselves active and nonactive respectively. The animals in these groups were matched according to body weight to the animals in the PTU-active and PTU-nonactive conditions, and for the entire duration of the experiment remained matched with regard to food intake.

The experiment was run in a separate air conditioned (21–23°C) room in which a 12/12 hr light/dark cycle was operating. Food and water were replenished at precisely the same time each day, when the following data were collected: activity, body weight, and food intake. Except for the two pairfed controls all animals received chow ad lib. All animals had free access to water.

The experiment consisted of the following two phases: (1) After adaptation in the experimental room for 8 days, PTU treatment began, and lasted 43 days. Activity wheels were opened 3 days after the beginning of drug treatment in order to eliminate the risk of death in animals of small age. (2) A recovery phase followed the drug period and lasted 75 days. During this phase PTU was discontinued and the wheels were closed. The two pairfed controls remained in pairfeeding condition unless the animal to which they were "yoked" ate less or equal to what they were eating; in those cases food was given ad lib. on days 76 and 77 of the recovery phase all animals were killed with an overdose of anaesthetic, the right tibia exposed, and its length measured with calipers.

The data from the four groups of the factorial design were analyzed by analysis of variance. Comparisons with the pairfed controls were done by applying the t-test for matched observations.

RESULTS

A summary of the results is given in Table 1. Although the activity of PTU treated rats was higher on the average this difference was not significant ($p>0.10$, data from the last 20 days of PTU treatment). The pairfed controls ran significantly more than the PTU animals ($p<0.002$). On the last day of the drug-treatment phase the PTU animals weighed significantly less than the ad lib euthyroid controls ($p<0.001$). Neither the activity nor the interaction terms were significant. Pairfed controls in the active condition weighed less than their PTU counterparts ($p<0.01$). After 75 days of recovery the PTU animals still weighed less then euthyroid controls ($p<0.001$), but no difference existed between PTU and pairfed conditions ($p>0.20$). These findings are in accord with the tibia linear growth data. The tibiae of the PTU recovered animals were significantly shorter than those of ad lib feeding euthyroid controls ($p<0.001$), but no different from those of pairfed animals ($p>0.40$).

During the phase of drug administration PTU animals ate significantly less than euthyroid ad lib controls ($p<0.001$). Activity had no effect on food intake.

DISCUSSION

The activity of male rats made hypothyroid by consuming PTU was not significantly different from the activity of euthyroid, ad lib feeding controls. This is in agreement with the findings reported by some of the early studies on thyroidectomized animals [12,13], and also animals with drug-induced hypothyroidism [9,15]. The decrease in activity that was reported by two early studies in which animals were thyroidectomized [11,19] may have been due to postoperative complications or parathyroid insufficiency, a condition that would be expected to influence adversely neuromuscular function and general health [10,24]. Leshner and Walker's [15] data indicate a decrease in the activity of

self-selecting hypothyroid rats, a finding that may be peculiar to the synthetic diet used in that study. Alternatively, it may well be that self-selecting hypothyroid group appears hypoactive only because control animals are hyperactive: the latter animals not only exhibit unusually high levels of activity in comparison to the euthyroid rats in this investigation as well as other studies [4, 14, 17], but also maintained their body weight at a lower level in comparison to nonactive controls. This does not agree with data on control animals in previous studies [14,17].

While no reduction in the activity of hypothyroid rats is evident when an ad lib, euthyroid control is used, a comparison with a pairfed, non-drugged control shows lower levels of activity in PTU treated animals. Non-drugged food restricted animals are hyperactive [3]. It should be pointed out, however, that the above conclusions should be taken with caution since body weight loss rather than food intake seems to be related to degree of activity [3]. As already mentioned the pairfed control in the active condition maintained a lower body weight in comparison to PTU animals. Further experiments are needed in which body weight rather than food intake is kept matched.

It may be of interest to speculate why growth arrest by chemical means [9, 15, 17] does not result in hyperactivity, while growth arrest by food restriction leads ot high levels of activity. The obvious difference in these two manipulations is that food-restricted animals are hungry while monosodium glutamate [17] or PTU treated animals feed ad lib. Hypothyroidism is also associated with changes in a host of physiological parameters: e.g. reduced rates of somatotropin synthesis [25], lower level of plasma corticosterone [6], involution of adrenals [27], altered liver physiology [26], higher levels of serum cholesterol [22] and thyroid stimulating hormone [26], and lowered metabolic rate [2]. The general physical condition of the animal is poor: the reported leucopenia [22] indicates greater susceptibility to infections, while muscle weakness [18] and diminished work capacity [16] would be expected to influence locomotion adversely. It is therefore exceedingly hard to discern a single pathway through which behavioral effects are mediated. It is likely that a dynamic state of affairs exists among variables such as the ones mentioned. Further, since none of the above changes is known to contribute to hyperactivity, and some of them are known to be associated with hypoactivity (e.g. [14,16], the proper question to be asked may be "what prevents the hypothyroid rat from being hypoactive." In this connection it is likely that the increased levels of TSH and possibly thyrotropin-releasing factor [20,24] along with other CNS changes due to absence of thyroid hormones may result in an excitatory central effect [1] that counteracts peripheral changes that would inhibit locomotion (e.g muscle weakness, adrenal insufficiency, see [14]).

Severe growth arrest, as evidenced by low body weights and infantile shape cranium, occurred in the PTU animals during the 43 days of drug feeding. Histological and physiological details of the nature of this growth suppression have been reported elsewhere [5,22]. Recovery studies have pointed to the importance of age at the time of treatment [2,7]. In the present study PTU feeding took place during a period characterized by maximum growth rate [21]. Dearden and Mosier [5] using male rats of the same age and administering the same dose of PTU as in the present study inhibited growth for 18 days. After 26 days of recovery they observed that catch-up growth (as indicated by tibial linear growth) was not complete. This is in agreement with the findings reported here: growth arrest was still evident after 75 days of recovery.

No difference in catch-up growth indices (tibial length and body weight) of PTU treated and pairfed non-drugged animals was noted. While the direct effects of thyroxine on chondrocytes and ossification should not be overlooked [8, 21, 23], this study indicates that indirect effects stemming from altered behavior (such as feeding) may have been underestimated to date.

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