Introduction

Hypothyroidism is an endocrine disorder that results from decreased levels of the hormone thyroxine in the body's tissues, lowering the body's metabolic rate and slowing growth due to the consequent decreased interaction of thyroxine with growth hormones (Widmaier et al., 2008). The normal negative feedback loop of thyroxine level regulation lies in the response of the anterior pituitary and hypothalamus to thyroxine and the adjustment of thyroid-releasing hormone (TRH) and thyroid-stimulating hormone (TSH) levels, respectively (Widmaier et al., 2008). When there is a defect in the feedback loop, certain hormones increase in the circulation while others decrease. This is true for hypothyroidism, which can be caused by a mutated TSH receptor on the thyroid gland, and thus will affect the blood hormone levels by raising the concentration of TSH and lowering the concentration of thyroxine in the circulation (Beamer *et al*, 1981).

In this experiment, we studied the effect of hypothyroidism on the growth of two populations of hypothyroid weanling C·RF mice as compared to a control population. To induce hypothyroidism, one population was fed 6-*n*-propyl-2-thiouracil (PTU) in its diet, a substance known to block iodide uptake into the thyroid and thus interfere with thyroxine synthesis (Widmaier et al., 2008) and the second population contained a gene for hypothyroidism, *hyt/hyt*, a genotype discovered by Beamer and co-workers (1981).

Materials and Methods

Three litters of C·RF mice were housed separately: five male control mice, five female mice fed 6-*n*-propyl-2-thiouracil (PTU) in their diet, and two *hyt/hyt* male mice. Mice were weighed weekly to 0.1 gram beginning during the week of their weaning and continuing for

eleven weeks. PTU was fed at a concentration of 5 mg PTU/gm of food to induce hypothyroidism.

Results

Over the 11-week period, the *hyt/hyt* population exhibited the least amount of weight gain, with the lowest growth rate (Fig. 1, 2, 3, 4). The PTU-treated population grew more than the *hyt/hyt* group, but to a lesser amount than the control population (Fig. 1, 2, 3, 4).

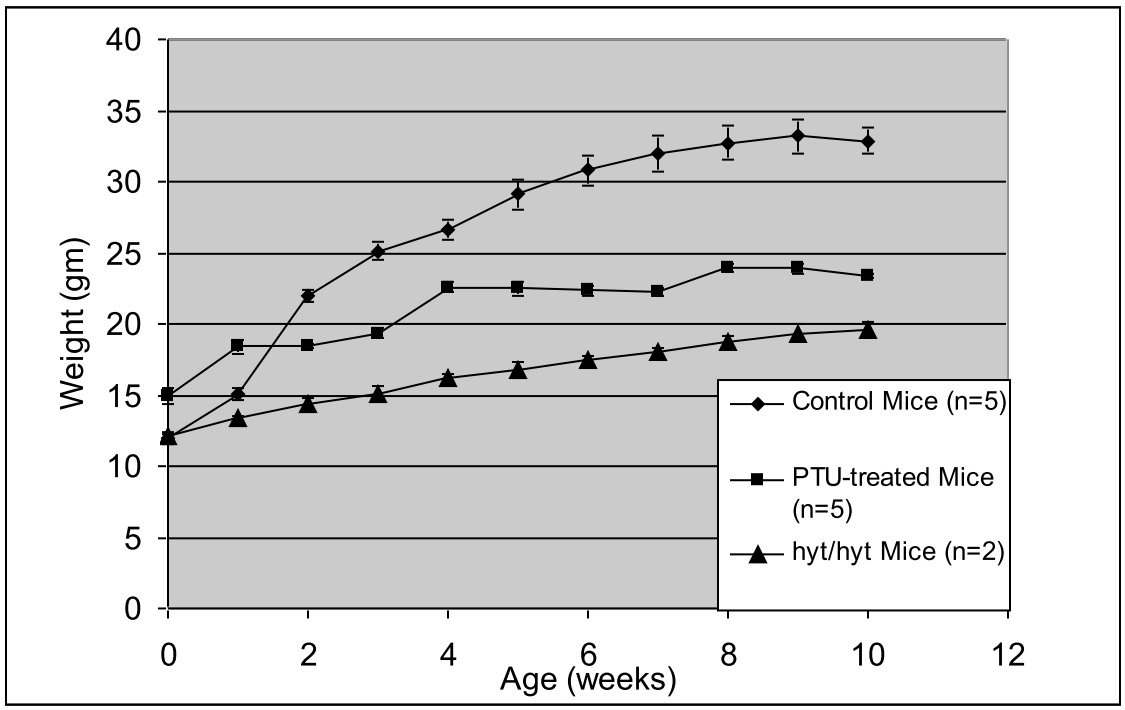

Figure 1.Tuesday Lab Section Data: The effect of the *hyt/hyt* genotype and incorporation of PTU into the diet on the growth of CRF mice. Values represent mean ± SEM for number of mice specified.

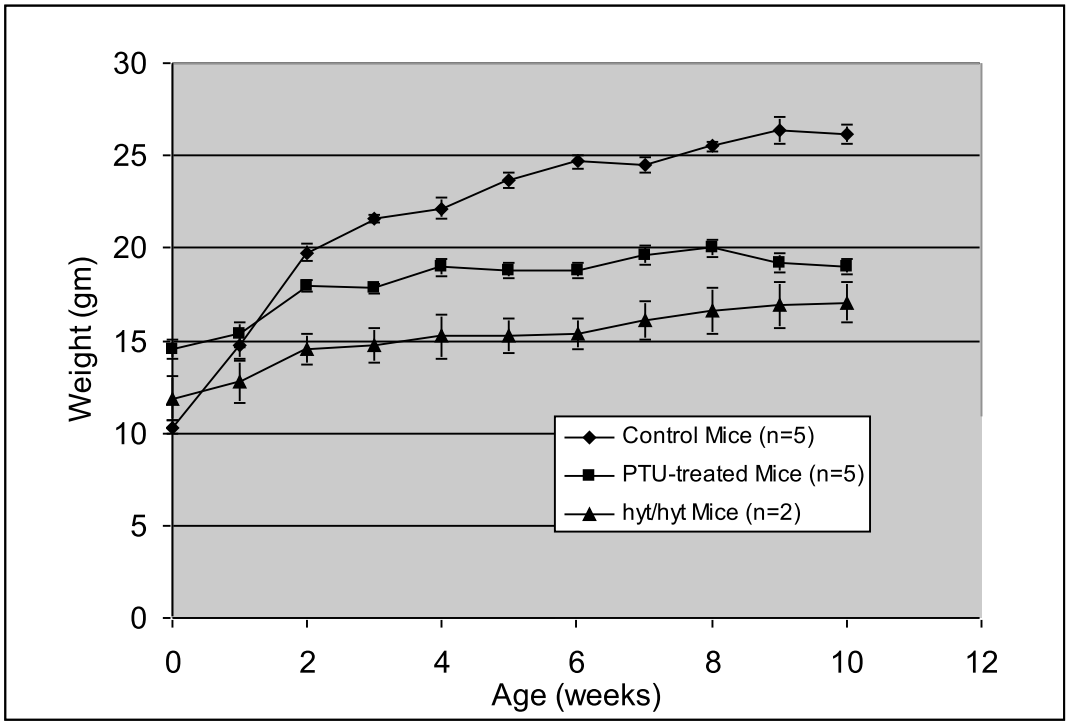

Figure 2.Wednesday Lab Section Data: The effect of the *hyt/hyt* genotype and incorporation of PTU into the diet on the growth of CRF mice. Values represent mean ± SEM for number of mice specified.

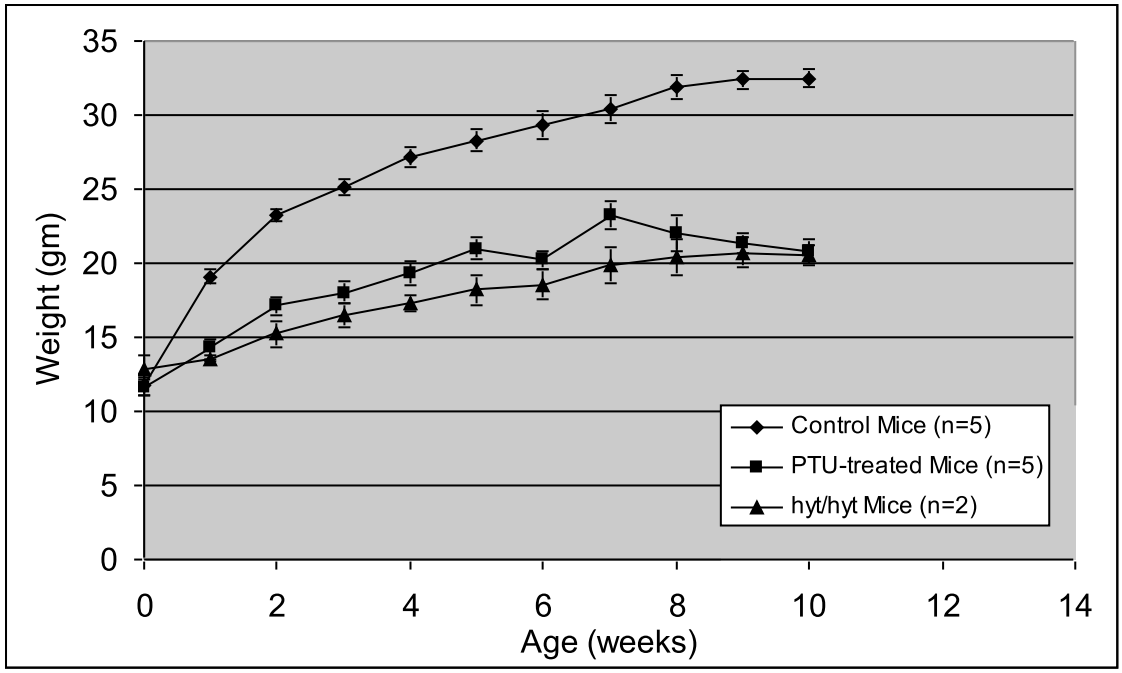

Figure 3.Thursday Lab Section Data: The effect of the *hyt/hyt* genotype and incorporation of PTU into the diet on the growth of CRF mice. Values represent mean ± SEM for number of mice specified.

The average combined data from the three lab sections indicates a growth rate of 0.6817 gm/week in the *hyt/hyt* population, approximately half the rate of the control population (1.7393 gm/week). The PTU-treated grew only slightly more quickly than the *hyt/hyt* group (0.7083 gm/ week).

During the first week, the difference between the average weights of the PTU-treated and those of the control groups for the combined lab sections was 2.3806 gm. By the eleventh week, the difference was 9.4242 gm. By week five, a significant difference had developed between the two populations (5.0438 gm).

The difference between average weights of the *hyt/hyt* and control populations was initially 0.92393 gm. By week 11, however, the difference was 11.43103 gm. A difference of 6.9734 gm had already appeared by the third week.

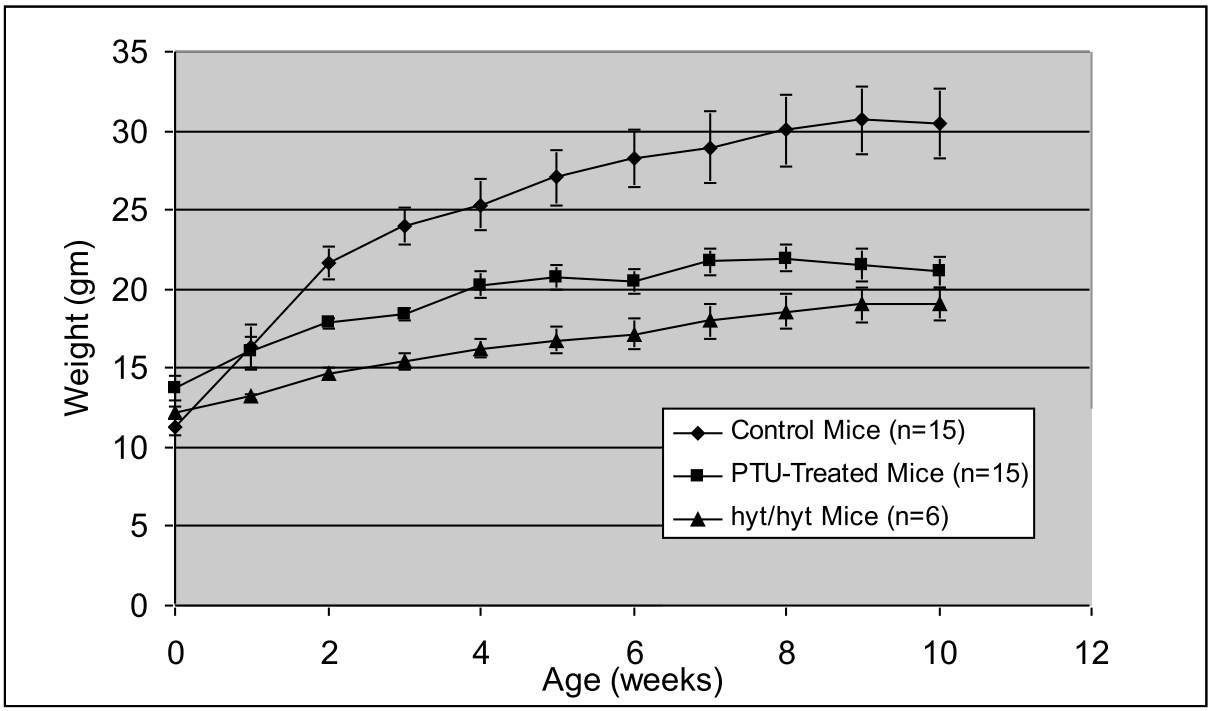

Figure 4. Combined Lab Section Data: The effect of the *hyt/hyt* genotype and incorporation of PTU into the diet on the growth of CRF mice. Values represent mean ± SEM for number of mice specified.

Table 1. T -test results using the weights of PTU-treated and control CRF mice at 0 and 10 weeks of age.

	0 week old t-value	0 week old p-value	0 week old t-value	10 week old p-value
Tuesday Lab Section	4.3930	0.0023	10.4203	0.0001
Wednesday Lab Section	6.3979	0.0002	10.7081	0.0001
Thursday Lab Section	0.0813	0.9372	12.4305	0.0001

Table 2. T-test results using the weights of *hyt/hyt* and control CRF mice at 0 and 10 weeks of age.

	0 week old t-value	10 week old p-value	0 week old t-value	10 week old p-value
Tuesday Lab Section	0.3091	0.7697	8.6039	0.0003
Wednesday Lab Section	1.6473	0.1604	8.8227	0.0003
Thursday Lab Section	0.9335	0.3934	11.6984	0.0001

Statistical analysis with t-tests supports the graphical data and trends in increasing weight differences between the groups as time progressed, indicating significant diversion of growth between both the control and PTU-treated and control and *hyt/hyt* populations.

Discussion

The control of thyroxine originates in the hypothalamus, with the release of thyrotropin-releasing hormone (TRH) to the pituitary gland, which then signals the release of thyroid-stimulating hormone (TSH) (Widmaier et al., 2008). TSH binds to the thyroid gland's follicular cells, stimulating the release of thyroxine in its T_4 form (T_4 is converted to T_3 in the target cell tissues) (Widmaier et al., 2008). Because there are a total of three hormones involved in this feedback loop, there are three potential stages in which a malfunction could cause

hypothyroidism (Beamer *et al*., 1981). Primary hypothyroidism occurs in the follicular cells themselves, with malfunctions that impede the normal production of thyroxine; secondary hypothyroidism occurs in the pituitary gland, with an abnormally low production of TSH; tertiary hypothyroidism occurs in the hypothalamus, with an unusually low production of TRH (Beamer *et al*., 1981). The *hyt/hyt* mouse model is an example of primary hypothyroidism, because there is a desensitization of thyroid follicular cells to TSH, indicating a mutation of the TSH receptor on the plasma membrane (Beamer *et al.,* 1981). Indeed, de Felice and co-workers (2004) found that *hyt/hyt* mice have a defective gene for the TSH receptor, T*shr*, which replaces a proline with a leucine residue and therefore disrupts the binding affinity of TSH to the active site. TSH is essential to thyroxine synthesis, because it mediates the uptake of iodide into the follicular cells for its incorporation into tyrosine residues that become thyroxine (de Felice *et al.* 2004; Widmaier et al., 2008).

Because a negative feedback loop exists between TRH, TSH, and T_4 (Widmaier et al., 2008), a mutation in the TSH receptor that causes a decrease in thyroxine release will cause the pituitary to product more TSH, raising the levels in the blood (Green et al., 1988). Green and co-workers (1988) reported that blood TSH levels can occur at up to ten times the normal concentration of TSH usually found in the blood.

Mika *et al.* (1992) state that thyroxine functions with growth-hormone releasing factor (GRF) to promote growth; without thyroxine, growth hormone is not secreted, and development slows. This was evident in the *hyt/hyt* mouse populations studied in this experiment. The reduction of thyroxine most likely impaired the normal secretion of growth hormone that stimulates growth and development.

Likewise, the PTU-treated animals exhibited similar growth retardation. This is a result of the PTU, which is known as a goitrogen, a molecule that prevents the correct uptake of iodide into the follicular cells to synthesize thyroxine (Widmaier et al., 2008). Therefore, the PTU-treated mice are in essence experiencing the same effect as the hyt/hyt mice: the normal uptake of iodide into their thyroid glands is impaired, and therefore normal thyroxine synthesis cannot take place.

References

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