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Inhibin B Levels in Hypothyroid Males

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Background: The primary role of inhibin B is the regulation of gametogenesis via negative feedback on the production of follicle stimulating hormone (FSH) by the pituitary.
Methods: We studied 14 males with primary hypothyroidism due to various etiologies to determine if they exhibited hypogonadotrophic hypogonadism involving the reproductive segment of the gonadotrophic axis. Levels of inhibin B, FSH, luteinizing hormone, testosterone, free thyroxine, and thyrotropin were measured.
Results: The mean level of inhibin B in males with primary hypothyroidism was found to be approximately half that of normal males. The FSH level remained within the normal range and no reciprocal increase was observed as occurs in other conditions with reduced inhibin B.
Conclusions: Our results indicate that primary hypothyroidism has a significant effect on inhibin B levels without reciprocal increase in FSH, which is consistent with a hypogonadotrophic hypogonadal state affecting the reproductive segment of the gonadotrophic axis.

Introduction

Primary hypothyroidism results in widespread abnormalities, with all body systems affected. The effects on the hypothalamus anterior–pituitary axis are well recognized, with abnormalities in secretion of growth hormone, adrenocorticotrophic hormone (ACTH), prolactin, and gonadotrophins. Inhibin B is secreted by Sertoli cells in males and by the granulosa cells of the ovary in females. Inhibin B is primarily under the control of follicle stimulating hormone (FSH) and has been shown to have a reciprocal relationship with FSH in men with various testicular disorders. We therefore studied 14 males with primary hypothyroidism to assess the impact of primary hypothyroidism on the hypothalamic–pituitary–Sertoli cell axis.

Materials and Methods

Fourteen blood samples from males with primary hypothyroidism, aged 23 to 69 years, median age 44 years, were studied. The hypothyroid state of the 14 patients was caused by thyroxine (T_4) withdrawal for assessment of thyroid cancer in two patients, by radioiodine treatment of nodular thyroid disease or Graves' disease in four, by autoimmune thyroiditis in seven, and secondary to surgery for benign thyroid disease in one. The normal controls were euthyroid male patients without pituitary–testicular disorder or any other medical disorder.

Hormone assays

All samples were assayed together to eliminate interassay variability. Inhibin B was measured using an enzyme-linked immunosorbent assay by DSL-10-84100 (Diagnostic Systems Laboratory, Webster, TX) with a minimum detection limit of 5 pg/mL, interassay coefficient of variation (CV) 6.2% and intraassay CV of 5.6%, and reference range 60–271 pg/mL.

FSH was measured by a microparticle enzyme immunoassay using the automated Abbott AxSYM (Abbott Laboratories, Diagnostic Division, Abbott Park, IL) with an analytical sensitivity of 0.05 IU/L, interassay CV of 3.6% and intraassay CV of 2.50%, and reference range for males of 1.0–8.0 IU/L.

Luteinizing hormone (LH) was measured by a microparticle enzyme immunoassay using the automated Abbott AxSYM with analytical sensitivity of 0.07 IU/L, interassay CV of 3.70% and intraassay CV of 2.5%, and reference range for males 2.0–10.0 IU/L.

Thyrotropin (TSH) was measured by a chemiluminescence immunoassay using Siemens Immulite 2000 (Siemens Medical Solution Diagnostics, Los Angeles, CA) with an analytical sensitivity of 0.004 mIU/L, interassay CV of 5.10% and intraassay CV of 5.10%, and reference range 0.5–4.0 mIU/L.

Free T_4 was measured by a microparticle enzyme immunoassay using the automated Abbott AxSYM with analytical sensitivity of 5.1 pmol/L, average interassay CV of 4.8% and intraassay CV of 3.8%, and reference range 10–20 nmol/L.

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Testosterone was measured using a chemiluminescence immunoassay of Siemens Immulite 2000, with analytical sensitivity 0.7 nmol/L, interassay CV 10.3% and intraassay CV of 10%, and reference range for males of 10.0–30.0 nmol/L.

Results

The mean level of inhibin B in males with primary hypothyroidism was 87 ± 14 pg/mL, which was significantly reduced from the mean level of 158 ± 9 pg/mL for normal males. The difference between the mean inhibin B level in primary hypothyroid patients and normal subjects was 71 ± 16 pg/mL. The magnitude of the difference was more than four standard deviations and was highly significant, $p < 0.00001$. The mean FSH value in the primary hypothyroid group at 6.1 ± 0.9 mIU/L remained in the normal range. LH and testosterone levels were reduced in the hypothyroid subjects as compared to euthyroid controls, and thyroid function tests were consistent with marked hypothyroidism. Results are presented in Table 1.

Discussion

Primary hypothyroidism has effects on numerous organ systems, and the effects on the hypothalamic–pituitary function are well recognized (1).

Growth hormone secretion is reduced, and the response to provocative testing including insulin hypoglycemia (2) and sleep-induced growth hormone is reduced (3). Growth hormone mRNA is subnormal in hypothyroid rats (4), and triiodothyronine (T_3) increases the expression of the promoter of the rat growth hormone gene (5). Cortisol levels in primary hypothyroidism are normal (6) due to reduced metabolic clearance, but hyposecretion of ACTH and cortisol has been reported (5).

Prolactin levels in primary hypothyroidism, while frequently reported as elevated, are rarely, if ever increased in males. Of particular interest is the normal 24 hour mean prolactin profile reported in males with primary hypothyroidism (7–11).

Primary hypothyroidism has significant effects on the hypothalamic–pituitary–gonadal axis in females and males (12). Thyroid hormone increases the production of plasma sex hormone binding globulin (SHBG) indirectly by increasing HNF-4α, but SHBG levels are low in hypothyroidism (13). As a result, total testosterone levels are low in hypothyroidism. Moreover, free testosterone levels are lower in hypothyroidism and increase after T_4 replacement (11).

The finding of normal LH and FSH levels in conjunction with blunted gonadotrophin responses to gonadotrophin-releasing hormone (GnRH) indicates that primary hypothyroidism impairs the ability of the pituitary gland to respond to GnRH (12). Support for this finding "is that hCG produces an exaggerated response of serum testosterone" (12) indicating that Leydig cell response is maintained and suggesting that primary hypothyroidism is creating a hypogonadotrophic hypogonadal state.

Support for the effect of hypothyroidism on hypothalamic–pituitary function giving rise to hypogonadotrophic hypogonadism is present in animal studies. Hypothyroid rats have been reported as having reduced GnRH and thus pituitary gonadotrophin biosynthesis, secretion, or both are impaired (14). The pituitary contents of LH are reduced in hypothyroid rats (15), and in hypothyroid rams LH levels are low and the LH response to LHRH is reduced (16).

While the main effect of primary hypothyroidism seems to be at the level of the hypothalamus–pituitary, primary hypothyroidism has effects on the testis. Thyroid hormone receptors have been reported in the testis (17); T_3 stimulates Sertoli cell function and mRNA expression of inhibin B and regulates Leydig cell function as well. In humans, hypothyroidism has effects on spermatogenesis with morphological changes and alteration in sperm motility (18). In rats, hypothyroidism results in arrested proliferation of germ cells (19) and in hypothyroid rams in reduced sperm motility (18).

It is well recognized that an intricate network of paracrine and autocrine systems exists in the testis (20). If hypothyroidism was acting at the level of the testis either directly or by affecting autocrine/paracrine function, one would expect a reciprocal increase in gonadotrophins.

Inhibin B is secreted by the Sertoli cells of the testis and is under the control of FSH (21). Extensive studies in humans and primates have consistently concluded that inhibin B plays a major role in the restraint of GnRH-stimulated pituitary FSH secretion (22). It has been shown that inhibin B is the principal gonadal feedback regulator of FSH (23).

However, in hypothyroid males, testosterone and free testosterone are low and estradiol levels are normal (18,24) and have no apparent impact on gonadotrophin secretion because there is no reciprocal increase in FSH and LH. In sheep and rats, inhibin B suppresses FSH synthesis and secretion (25,26).

This is the first report on inhibin B levels in males with primary hypothyroidism. The mean inhibin B level being approximately half that of normal males (87 ± 13 pg/mL versus 158 ± 9 pg/mL). Associated with this is the expected reduction in serum testosterone levels. The LH and FSH levels remaining in the normal range indicate that the hypothyroid

Table 1. Mean Levels and Standard Deviations of Inhibin B, Thyrotropin, Free Thyroxine, Follicle Stimulating Hormone, Luteinizing Hormone, and Testosterone in Normal Euthyroid Males and Hypothyroid Males

	Normal	*Primary hypothyroid*	p *values of difference*	*Units*
Inhibin B	158 ± 9	87 ± 14	<0.00001	pg/mL
TSH	2.5 ± 0.5	143 ± 34	<0.00002	mIU/L
Free T_4	16.7 ± 1.0	5.9 ± 0.3	$<10^{-10}$	pmol/L
FSH	6.9 ± 0.7	6·1 ± 1.0	<0.45	IU/L
LH	5.6 ± 0.5	3.0 ± 0·3	<0.00001	IU/L
Testosterone	18.5 ± 2.9	10.6 ± 1.0	<0.03	nmol/L

TSH, thyrotropin; T_4, thyroxine; FSH, follicle stimulating hormone; LH, luteinizing hormone.

state was acting at the level of the hypothalamus–pituitary. While systemic illness can cause hypogonadotrophic hypogonadism, these patients had no coexisting illness.

Conflicting reports of testosterone levels with low (27) and normal testosterone (28,29) in sleep apnea have been reported. However, there was no evidence of sleep apnea in our subjects either through questioning the subject and spouse or by applying the Epworth scale since hypothyroidism is a recognized cause of sleep apnea.

In a small pilot study [Donnelly P, Tan K, Winch D (2012), unpublished data] with five samples from partially treated hypothyroid subjects with resultant subclinical hypothyroidism, there was no increase in inhibin B levels but more than a 60% increase and normalization of testosterone levels in all patients in the presence of normal LH and FSH levels, suggesting a dichotomy in recovery of testosterone and inhibin B.

Our subjects with primary hypothyroidism fulfill the criteria for hypogonadotrophic hypogonadism in that "both the FSH and LH levels are inappropriately low given the subnormal sex-steroid levels" (30) and they had markedly reduced inhibin B levels. Our results support the hypothesis that primary hypothyroidism has a significant influence on hypothalamic–pituitary–gonadal function, and the hypothyroid state causes the reproductive segment of the gonadotrophic axis at the level of the hypothalamus–pituitary to reduce inhibin B levels by a factor of 50%.

Disclosure Statement

The authors declare that no competing financial interests exist.

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