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The Effect of Short-Term Hypothyroidism on Growth Hormone Secretory Responses To Growth Hormone-Releasing Hormone (1-29) and Insulin-Induced Hypoglycemia

Dimitris Mytilinaios,[1] Elena Nikolopoulou,[1] Antonia Charchanti,[2] Theodore Troupis,[1] Themis C. Kamilaris,[3] Elizabeth O. Johnson[1*]

[1]Department of Anatomy, Laboratory for Education & Research in Neurosciences (LERNs), National & Kapodistrian University of Athens, School of Medicine, Athens, Greece
[2]Department of Anatomy-Histology-Embryology, University of Ioannina, School of Medicine, Ioannina, Greece
[3]Department of Endocrinology and Metabolism, Agia Marina Hospital, Institute of Social Security, Athens, Greece

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***Address for correspondence:**

Professor Elizabeth O. Johnson,

Laboratory for Education & Research in Neurosciences (LERNs), Department of Anatomy, National and Kapodistrian University of Athens, School of Medicine Mikras Asias Str #75, Goudi 11527 Athens, Greece

Ph no: +30-210-746-2349

Email: elizabethojohnson@gmail.com

ABSTRACT

Introduction: Hypothyroidism is frequently associated with growth failure. In long-standing hypothyroidism the growth hormone (GH) secretory responses to growth hormone-releasing hormone (GRH) and insulin-induced hypoglycemia are decreased. **Methods:** To investigate whether hypothyroidism of short duration affects pituitary GH release, we measured the serum GH response to synthetic GRH (1-29), 1g/kg body weight, given IV to six athyreotic patients during thyroxine (T4) treatment and one month after stopping T4 (short-term hypothyroid state). This served as a direct measure of pituitary somatotroph function .We also assessed the serum GH response to insulin-induced hypoglycemia in three patients as an indirect assessment of hypothalamic function. **Results:** We found that basal GH levels remained the same both during (euthyroid state) and after stopping T4 therapy (hypothyroid state). Peak serum GH response to GRH was significantly greater in patients while they were hypothyroid than during T4 therapy when they were euthyroid ($p < 0.01$). There was no difference in the peak serum GH response to hypoglycemia during and after stopping T4 replacement (30.3 + 8.9 g/L euthyroid-state versus 45 + 14.5 g/L short term hypothyroid-state). **Discussion:** These results suggest that, in contrast to long standing hypothyroidism, thyroid hormone deficiency of short duration increases somatotroph sensitivity to GRH, perhaps as a result of decreased endogenous hypothalamic IGF-1 release and/or tone.

Key words: hypothyroidism, growth hormone, IGF-1, thyroid hormone, athyreotic

INTRODUCTION

Thyroid hormones regulate normal utilization of energy and production of heat by the body. In addition to being critical direct biological regulators of normal growth and development, thyroxine (T4) and triiodothyronine (T3), influence and interact with the growth hormone (GH)- insulin-like growth factor-I (IGF-1) axis, as well as with other growth regulating hormones. Hypothyroidism is almost always associated with growth failure.IGF-1, referred to as somatostatin-C in the past, is a growth factor that functions in several metabolic pathways, that is secreted by the liver in response to GH. The pulsatile GH secretion is primarily regulated by the dynamic interaction between forward signals from hypothalamic GH-releasing hormone (GHRH) and ghrelin with feedback signals from IGF-1 and GH at both the level of the hypothalamus and pituitary.[1–5]

Thyroid hormones are also known to significantly affect GH secretion.[6–9] Hypothyroid patients and rats show low levels of plasma IGF-1, while hyperthyroid patients show high levels of plasma IGF-1.[10,11] Long-standing hypothyroidism in man and experimental animals results in low GHRH levels[6,12] and also in low basal GH levels.[13-16] Additionally, hypothyroidism has been shown to lead to decreased GH secretory responses to insulin-induced hypoglyce-

mia.[16,17] To date, it has been suggested that the impairment of GH secretion is related to the severity, but not the duration of hypothyroidism.[17,18] This is in contrast to studies in thyroidectomized rats in which changes in pituitary GH content and synthesis, as well as hypothalamic GHRH and SRIF content and synthesis, appeared to be related to the duration of hypothyroidism.[20]

The present study was designed to examine the effect of short-term hypothyroidism. This was achieved by assessing GH secretion in athyreotic patients while they were taking thyroid hormone suppressive therapy and one month after withdrawal from thyroid hormone. We used the serum GH response to synthetic GRH (1-29), a GRH fragment which exhibits full biological activity *in vivo*[21] and *in vitro*,[22] as direct measure of pituitary somatotroph function and the serum GH response to insulin-induced hypoglycemia as an indirect assessment of hypothalamic function. We hypothesized that thyroid hormone deficiency of short duration would affect GH secretion differently than that observed in long-standing hypothyroidism.

MATERIALS AND METHODS

Six athyreotic patients (1 man and 5 women) from the Agia Marina Hospital Endocrinology Clinic, Athens, Greece, participated in this study. Ages ranged from 30 to 63 years (mean, 45.3 yr) and body weight ranged from 60 to 83 kg. All patients had undergone suppressive therapy with sodium l-thyroxine (T4), 0.2 mg/day, for at least 2 years after having had a total thyroidectomy and radioiodine ablative therapy for thyroid carcinoma. Annual evaluations for 2 to 10 years follow-up with total body radioiodine scans were negative for local recurrence or distant metastases in all patients. Patients were taking no medications other than at the time of initial examination and all appeared clinically euthyroid. All patients had normal physical examinations and normal blood cell counts, serum chemistry profiles, urinalyses and electrocardiograms. There was no significant change in body weight in any of the patients during the interval between the two studies (during T4 therapy and one month after T4 therapy).

The clinical and laboratory characteristics of the 6 patients were studied during their annual evaluation. After giving their informed consent, the patients underwent GRH and insulin-induced hypoglycemia studies on different days on two occasions: first while taking T4 and again 1 month after stopping T4 treatment. After an overnight fast, an indwelling catheter was placed in a forearm vein at least 30 min before injection of GRH-(1-29), 1g/kg body weight, or regular insulin, 0.1U/kg body weight, between 0800 and 0900 h. Blood samples were obtained for GH and glucose at intervals from 15 min before until 120 min after hormone injection. The patients remained in a supine position throughout the hormone dynamic testing.

Serum GH was measured by liquid-phase RIA.[23]Serum TSH was determined by immunoradiometric assay (Corning Medical and Scientific, Medfield, MA). Serum total T4 (TT4) and total triiodothyronine (TT3) were determined by solid-phase RIA (Immunochem Corp., Carson, CA). Serum free

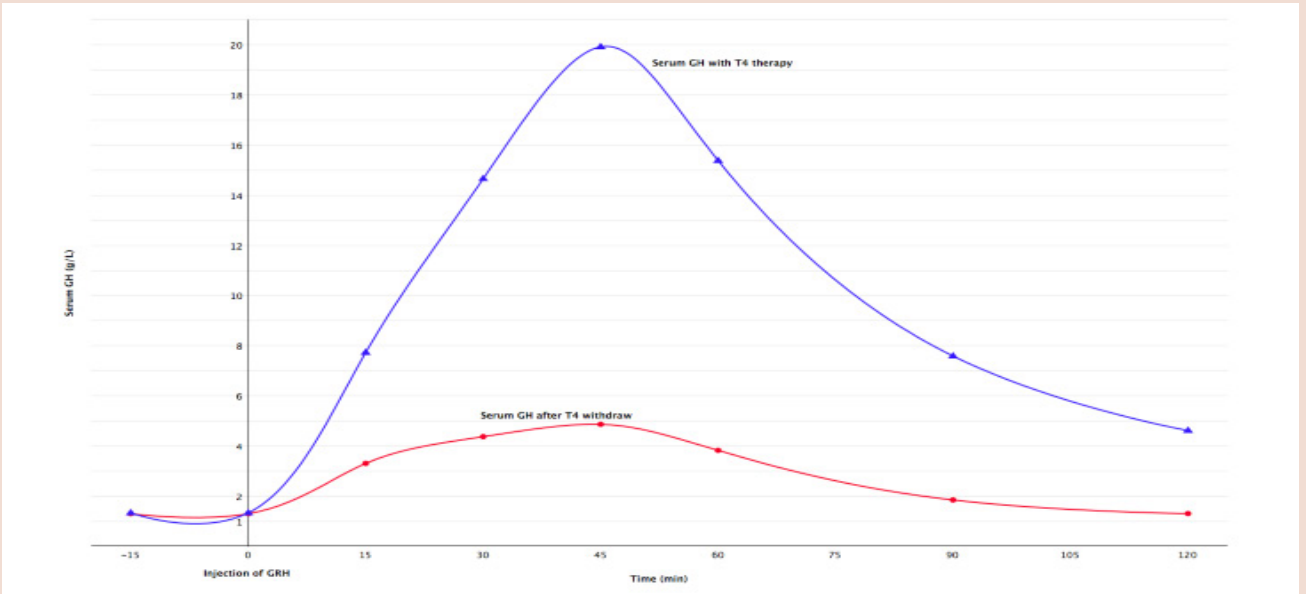


Figure 1: GR response to GRH administration during T4 therapy (euthyroid) and one-month after stopping T4 treatment (hypothyroid). While mean basal serum GH concentrations were similar in both groups, the serum GH response to GRH was significantly elevated in patients one month after stopping T4 therapy from 15 to 60 min after GRH administration. The mean peak GH concentration after GRH was significantly greater when the patients were short-term hypothyroid, compared when they were euthyroid (e.g. under T4 therapy).

T4 index (FT4I) and serum free T3 index (FT3I) were calculated using the TT4 and TT3 values, respectively, and the serum T4 resin uptake. Blood glucose was measured at the bedside with an automatic glucose analyzer.

Statistical comparisons were made using one-way analysis of variance (ANOVA) followed by Duncan's multiple range test or paired Student's t-test, when appropriate. Integrated serum GH responses were determined by calculating the area under the response curve and above the baseline level. The data are expressed as mean ± SEM.

RESULTS

While taking T4 all patients had low serum TSH concentrations, two patients had elevated TT4 levels and one had a borderline high FT4I, but all patients had normal TT3 and FT3 levels. None of the patients appeared to be clinically hyperthyroid. One month after stopping T4 therapy, serum TSH concentrations had risen to greater than 36mU/L and FTI had fallen to a very low level in every patient, but total and free thyroid hormone levels, which had fallen to very low levels in one patient were still at the lower limits of normal in the others. None of the patients appeared to "be overtly clinically hypothyroid.More specifically, the glucose nadir after regular insulin, 0.1 U/kg iv, was 1.16 ± 0.3 mmol/L (mean ± SEM) during and 0.9 ± 0.1 mmol/L after stopping T4 therapy. Serum TSH increased from 0.8 ± 0.3 mU/L (normal range, 0.5 - 4.9 mU/L) during T4 therapy to 140 ± 43 mU/L after stopping therapy. Serum total T4 (TT4), free T4 index, total TT3 and free T3 index levels fell from 174 ± 19 nmol/L, 1.3 ± 0.05 nmol/L, 2.4 ± 0.05 nmol/L and 41.8 ± 1.7 ng/dl (normal ranges, 59 - 154 nmol/L, 0.9 - 2.5 nmol/L, 1.2 - 3.1 nmol/L and 17 - 70 ng/dl, respectively) during T4 therapy to 21 ± 3.9 nmol/L, 0.3 ± 0.01, 1.0 ± 0.2 nmol/L and 17 ± 1.4 ng/dl, respectively, after T4 therapy was stopped. (Table 1)

Mean basal serum GH concentrations were similar during and one month after stopping therapy (1.3 g/L). One month after stopping T4 therapy, serum GH concentrations from 15 to 60 min after injection of GRH were significantly greater than during therapy. The mean peak GH concentration after GRH was also greater one month after stopping T4 therapy than during T4 therapy (20 g/L). (Figure 1) Some patients noticed transient, mild facial warmth after GRH injection both during and after stopping T4 therapy.

The administration of insulin either during T4 or one month after stopping T4 therapy, resulted in no differences in the onset of hypoglycemia (15 min after insulin injection), serum glucose nadir (1.2 ± 0.1 nmol/L) and duration of hypoglycemia (30-45min). The initial rate that serum GH increased was similar in both groups. Both treatment groups reached a peak response between 45 to 60 min after insulin injection. In addition, there was no difference between the mean peak GH levels (30.3 ± 5.3 vs 45 ± 14.5 g/L) or integrated areas under the GH response curve (AUC) in the patients while under thyroid hormone therapy or one month after stopping therapy. Serum GH levels at 120 min were greater (<0.05) one month after T4 was stopped, compared to during T4 therapy. All patients experienced symptoms of hypoglycemia during both studies.

DISCUSSION

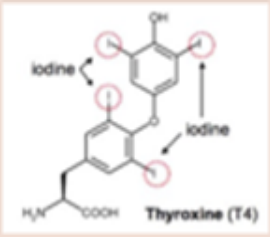
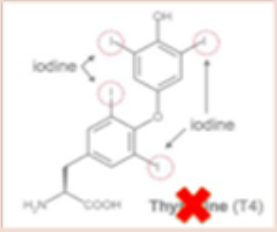
We report that short-term hypothyroid patients demonstrate increased somatotroph responsiveness to GRH, while the GH response to insulin-induced hypoglycemia remained unchanged. These observations differ from those reported in patients with long-standing, clinically severe hypothyroidism whose GH secretory responses to GRH and insulin-induced hypoglycemia were significantly blunted.[24,25]

These differences suggest that the effects of thyroid hormone deficiency on GH secretion are time dependent. This is similar to our previous findings that show that alteration in the hypothalamic-pituitary-adrenal axis function in states of disturbed thyroid function were dependent on the duration of thyroid dysfunction, with generally more pronounced effects as the duration of thyroid dysfunction increased.[26-29] Some of our patients were receiving greater than replacement dosages of, T4 as indicated by their relatively high TT4 levels and low TSH levels. However, the mean peak serum GH response to GRH during T4 therapy was not significantly different from that reported in normal, non-obese adults.[24]

Table 1: Thyroid hormone levels

Measure treatment	During T4 treatment (Euthyroid)	1 month after stoping T4 (short term hypothyroid)	Normal ranges
Glucose nadir (after regular insulin, 0.1 U/kg iv)	1.16 + 0.3 mmol/L	0.9 + 0.1 mmol/L	
Serum TSH	0.8 + 0.3 mU/L	140 + 43 mU/L	0.5 - 4.9 mU/L
Serum total T4 (TT4)	174 + 19 nmol/L	21 + 3.9 nmol/L	59 - 154 nmol/L
Free T4 index	1.3 + 0.05 nmol/L	0.3 + 0.01 nmol/L	0.9 - 2.5 nmol/L
Total TT3	2.4 + 0.05 nmol/L	1.0 + 0.2 nmol/L	1.2 - 3.1 nmol/L
Free T3 index	41.8 + 1.7 ng/dl	17 + 1.4 ng/dl	17 - 70 ng/dl

Table 2: GH hormone response after GRH stimulation and Insulin-induced hypoglycaemia tests.

	Measurements					
	WITH T4	**Number of patients**	**%**	**STOP T4**	**Number of patients**	**%**
						
	↓ serum TSH	6/6	100%	↑↑ serum TSH (> 36mU/L)	6/6	100%
Thyroid Hormone Levels	↑ TT4	2/6	33%	↓ TT4	1/6 (normal in 5/6)	16%
	↑ FT4I	1/6	16%	↓ FT4I	1/6 (normal in 5/6)	16%
	− TT3	6/6	100%	↓ TT3	1/6 (normal in 5/6)	16%
	− FT3	6/6	100%	↓ FT3	1/6 (normal in 5/6)	16%
				↓ FTI	6/6	100%
	! NO hyperthyroid		100%	! NO hypothyroid		100%
GH concentration	− Basal serum GH (1.3g/L)	6/6	100%	− Basal serum GH (1.3g/L)	6/6	100%
	− serum GH from 15-60 min after GRH	6/6	100%	↑↑ serum GH from 15-60 min after GRH	6/6	100%
	− mean peak GH after GRH	6/6	100%	↑ mean peak GH after GRH (20g/L)	6/6	100%
	! transient, mild facial warmth		some	! transient, mild facial warmth		some
Insulin administration	− onset of hypoglycemia (15min after injection)	6/6	100%	− onset of hypoglycemia (15min after injection)	6/6	100%
	− serum glucose nadir (1.2 + 0.1 nmol/L)	6/6	100%	− serum glucose nadir (1.2 + 0.1 nmol/L)	6/6	100%
	− duration of hypoglycemia (30-45min)	6/6	100%	− duration of hypoglycemia (30-45min)	6/6	100%
	− GH increase rate	6/6	100%	− GH increase rate	6/6	100%
	−peak response (45-60 min after injection)	6/6	100%	− peak response (45-60 min after injection)	6/6	100%
	− peak GH levels (30.3 + 5.3 g/L)	6/6	100%	− peak GH levels (45 + 14.5 g/L)	6/6	100%
	− serum GH levels at 2h	6/6	100%	↑ serum GH levels at 2h	6/6	100%
	! symptoms of hypoglycemia		100%	! symptoms of hypoglycemia		100%

Although several studies have addressed the relationship between thyroid function and GH secretion, the interrelationships between thyroid hormones and GH-IGF axis is not fully understood. More recently, studies have focused on delineating the mechanism of changes in thyroid hormone levels with assessment of GH-mediated increase of peripheral T4 to T3 deiodination.[30-32] About 3 decades ago, demonstrated that hypothyroid patients had diminished IGF-1 levels.[25] This suggests that either hypothyroid patients have diminished GH secretion or that that hypothyroidism has direct effects

upon IGF-1 production. Recently, thyroid hormones have been shown to regulate growth hormone receptor (GHR) expression *in vivo*.[33]

Animal studies have indicated that there is a complete loss of pulsatile GH secretion a >99% reduction in pituitary GH content, a 50% reduction of hypothalamic GRH content, a >90% reduction in spontaneous GH secretion and a >95% impairment of the response to GRH in short-term hypothyroidism, but that pituitary GH content is decreased by only about half this amount and there is no change in GH release in short-term hypothyroidism.[34-36] Akin reported that GH-IGF axis was affected in patients with subclinical hypothyroidism and that T4 replacement prevented some of the abnormal axis function.[37] Children with hypothyroidism, show a significant decrease of GH responsiveness to Clonidine stimulation, and a decreased IFG-1 response to GH stimulation.[38]

Recent evidence supports that the effects of thyroid hormone on plasma IGF levels is only partially mediated by GH. Rather, it seems that IGF levels in altered thyroid states are mediated by either direct effects of thyroid hormone on IGF, or by other GH-independent pathways. In mature hypothyroid rats, serum IGF-1 levels are only partially corrected by GH, but are normalized by thyroid hormone replacement.[39] Moreover, T4 administration alone to hypophysectomized or thyroidectomized animals is capable of stimulating IGF-1 activity in the absence of GH.[34]A strong positive thyroid hormone-dependent correlation between thyroid hormone concentrations and IGF-1 levels was reported in thyroidectomized rats.[36]

CONCLUSION

Several mechanisms may play a role in the growth failure observed in hypothyroidism, including abnormalities of GH secretion, IGF-1 synthesis, among others. Our findings of an almost normal GH response in our short-term, mild hypothyroidism patient cohort further support that the effects of hypothyroidism on the GH-IGF-1 system are time-dependent and dose-dependent.

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None

CONFLICT OF INTEREST

Authors declare no conflict of interest

ABBREVIATIONS USED

GH : Growth Hormone ; GRH : Growth hormone releasing hormone ; IGF -1: Insulin-like growth factor-1 ;T4 :Thyroxine ; FT4 : Free thyroxine ; FT3 : Free triodothyronine ; TT4 Total thyroxine ; TT3 : Total triodothyronine ;T3 : Triiodothyronine ; TSH :Thyroid stimulating hormone

REFERENCES

1. Plotsky PM, Vale W. Patterns of growth hormone-releasing factor and somatostatin secretion into the hypophysial-portal circulation of the rat. Science. 1985;230(4724):461-3. https://doi.org/10.1126/science.2864742.
2. Robinson IC. Control of growth hormone (GH) release by GH secretagogues. Novartis Found Symp. 2000;227:206-20. Discussion 220–4.
3. Veldhuis JD, Anderson SM, Shah N, Bray M, Vick T, Gentili A, et al. Neurophysiological regulation and target-tissue impact of the pulsatile mode of growth hormone secretion in the human. Growth Horm IGF Res. 2001;11:S25-37. https://doi.org/10.1016/S1096-6374(01)80005-8.
4. Sato M, Takahara J, Fujioka Y, Niimi M, Irino S. Physiological role of growth hormone (GH)-releasing factor and somatostatin in the dynamics of GH secretion in adult male rat. Endocrinology. 1988;123(4):1928-33. https://doi.org/10.1210/endo-123-4-1928 PMid:2901340.
5. Pe-alva A, Baldelli R, Cami-a JP, Cerro AL, Micic D, Tamburrano G, et al. Physiology and possible pathology of growth hormone secretagogues. J Pediatr Endocrinol Metab. 2001;14(5):1207-12. Discussion 1261–2.
6. Katakami H, Downs TR, Frohman LA. Decreased hypothalamic growth hormone-releasing hormone content and pituitary responsiveness in hypothyroidism. J Clin Invest. 1986;77(5):1704-11. https://doi.org/10.1172/JCI112490 PMid:2871046 PMCid:PMC424578.
7. Miki N, Ono M, Hizuka N, Aoki T, Demura H. Thyroid hormone modulation of the hypothalamic growth hormone (GH)-releasing factor-pituitary GH axis in the rat. J Clin Invest. 1992;90(1):113-20. https://doi.org/10.1172/JCI115823 PMid:1634603 PMCid:PMC443069.
8. Devesa J, Lima L, Tresguerres JA. Neuroendocrine control of growth hormone secretion in humans. Trends Endocrinol Metab. 1992;3(5):175-83. https://doi.org/10.1016/1043-2760(92)90168-Z.
9. Behan LA, Monson JP, Agha A. The interaction between growth hormone and the thyroid axis in hypopituitary patients. Clin Endocrinol. 2011;74(3):281-8. https://doi.org/10.1111/j.1365-265.2010.03815.x PMid:20455887.
10. Burstein PJ, Draznin B, Johnson CJ, Schalch DS. The effect of hypothyroidism on growth, serum growth hormone, the growth hormone-dependent somatomedin, insulin-like growth factor, and its carrier protein in rats. Endocrinology. 1979;104(4):1107-11. https://doi.org/10.1210/endo-104-4-1107 PMid:436752.
11. Miell JP, Taylor AM, Zini M, Maheshwari HG, Ross RJM, Valcavi R. Effects of hypothyroidism and hyperthyroidism on insulin-like growth factors (IGFs) and growth hormone and IGF binding proteins. J ClinEndocrinol Metab. 1993;76:950-3. https://doi.org/10.1210/jcem.76.4.7682563 https://doi.org/10.1210/jc.76.4.950.
12. Downs TR, Chomczynski P, Frohman LA. Effects of thyroid hormone deficiency and replacement on rat hypothalamic growth hormone (GH)-releasing hormone gene expression in vivo are mediated by GH. Mol Endocrinol. 1990;4(3):402-8. https://doi.org/10.1210/mend-4-3-402 PMid:2111453.
13. Chernausek SD, Turner R. Attenuation of spontaneous, nocturnal growth hormone secretion in children with hypothyroidism and its correlation with plasma insulin-like growth factor I concentrations. J Pediatr. 1989;114(6):968-72. https://doi.org/10.1016/S0022-3476(89)80439-1.

14. Iwatsubo H, Omori K, Okada Y, Fukuchi M, Miyai K, Abe H, et al. Human growth hormone secretion in primary hypothyroidism before and after treatment. J Clin Endocrinol Metab. 1967;27(12):1751-4. https://doi.org/10.1210/jcem-27-12-1751 PMid:6060962.
15. Valcavi R, Valente F, Dieguez C, Zini M, Procopio M, Portioli I, et al. Evidence against depletion of the growth hormone (GH)-releasable pool in human primary hypothyroidism: studies with GH-releasing hormone, pyridostigmine, and arginine. J Clin Endocrinol Metab. 1993;77(3):616-20. https://doi.org/10.1210/jcem.77.3.8103770 https://doi.org/10.1210/jc.77.3.616 PMid:8103770.
16. Clausen N, Lins PE, Adamson U, Hamberger B, Efendić S. Counterregulation of insulin-induced hypoglycaemia in primary hypothyroidism. Acta Endocrinol. 1986;111(4):516-21. https://doi.org/10.1530/acta.0.1110516.
17. Brauman H, Smets P, Corvilain J. Comparative study of growth hormone response to hypoglycemia in normal subjects and in patients with primary myxedema or hyperthyroidism before and after treatment. J Clin Endocrinol Metab. 1973;36(6):1162-74. https://doi.org/10.1210/jcem-36-6-1162 PMid:4706204.
18. Thomas JV, Mezzasalma DFC, Teixeira AM, Campos LNR, Luescher JL, Beserra ICR, et al. [Growth hormone deficiency, hypothyroidism and ring chromosome 18: case report]. Arq Bras Endocrinol Metabol. 2006;50(5):951-6. https://doi.org/10.1590/S0004-27302006000500019 PMid:17160222.
19. Valcavi R, Jordan V, Dieguez C, John R, Manicardi E, Portioli I, et al. Growth hormone responses to GRF 1-29 in patients with primary hypothyroidism before and during replacement therapy with thyroxine. Clin Endocrinol. 1986;24(6):693-8. https://doi.org/10.1111/j.1365-2265.1986.tb01666.x.
20. Dieguez C, Jordan V, Harris P, Foord S, Rodriguez-Arnao MD, Gomez-Pan A, et al. Growth hormone responses to growth hormone-releasing factor (1-29) in euthyroid, hypothyroid and hyperthyroid rats. J Endocrinol. 1986;109(1):53-6. https://doi.org/10.1677/joe.0.1090053 PMid:2871123.
21. Vittone J, Blackman MR, Busby-Whitehead J, Tsiao C, Stewart KJ, Tobin J, et al. Effects of single nightly injections of growth hormone-releasing hormone (GHRH 1-29) in healthy elderly men. Metabolism. 1997;46(1):89-96. https://doi.org/10.1016/S0026-0495(97)90174-8.
22. Lance VA, Murphy WA, Sueiras-Diaz J, Coy DH. Super-active analogs of growth hormone-releasing factor (1-29)-amide. Biochem Biophys Res Commun. 1984;119(1):265-72. https://doi.org/10.1016/0006-291X(84)91647-4.
23. Glick SM, Roth J, Yalow RS, Berson SA. Immunoassay Of Human Growth Hormone In Plasma. Nature. 1963;199:784-7. https://doi.org/10.1038/199784a0 PMid:14071191.
24. Hervas F, Morreale de Escobar G, Escobar del Rey F, PozueloEscudero V. Dynamics of growth hormone secretion in patients with primary hypothyroidism, before and after treatment of thyroideal hormones. Rev Iber Endocrinol. 1976;23:263-73. PMid:951557.
25. Chernausek SD, Underwood LE, Utiger RD, Van Wyk JJ. Growth hormone secretion and plasma somatomedin-C in primary hypothyroidism. Clin Endocrinol. 1983;19:337-44. https://doi.org/10.1111/j.1365-2265.1983.tb00007.x.
26. Johnson EO, Kamilaris TC, Calogero AE, Gold PW, Chrousos GP. Experimentally-induced hyperthyroidism is associated with activation of the rat hypothalamic-pituitary-adrenal axis. Eur J Endocrinol. 2005;153(1):177-85. https://doi.org/10.1530/eje.1.01923 PMid:15994759.
27. Johnson EO, Kamilaris TC, Calogero AE, Konstandi M, Chrousos GP. Effects of short-and long-duration hypothyroidism on function of the rat hypothalamic-pituitary-adrenal axis. Journal of Endocrinol Investigation. 2012;36:104-10. PMid:22714027.
28. Johnson EO, Calogero AE, Konstandi M, Kamilaris TC, La Vignera S, Chrousos GP. Effects of short- and long-duration hypothyroidism on hypothalamic-pituitary-adrenal axis function in rats: in vitro and in situ studies. Endocrine. 2012;42(3):684-93. https://doi.org/10.1007/s12020-012-9714-z PMid:22695985.
29. Johnson EO, Calogero AE, Konstandi M, Kamilaris TC, La Vignera S, Chrousos GP. Effects of experimentally induced hyperthyroidism on central hypothalamic-pituitary-adrenal axis function in rats: in vitro and in situ studies. Pituitary. 2013;16(2):275-86. https://doi.org/10.1007/s11102-012-0417-5 PMid:22975847.
30. Jørgensen JO, Møller J, Skakkebaek NE, Weeke J, Christiansen JS: Thyroid function during growth hormone therapy. Horm Res. 1992;38(1):63-67. https://doi.org/10.1159/000182572.
31. Martins MR, Doin FC, Komatsu WR, Barros-Neto TL, Moises VA, Abucham J: Growth hormone replacement improves thyroxine biological effects: implications for management of central hypothyroidism. J Clin Endocrinol Metab. 2007;92:4144-53. https://doi.org/10.1210/jc.2007-0941 PMid:17785357.
32. Portes ES, Oliveira JH, MacCagnan P, Abucham J: Changes in serum thyroid hormones levels and their mechanisms during long-term growth hormone (GH) replacement therapy in GH deficient children. Clin Endocrinol (Oxf). 2000;53:183-9 https://doi.org/10.1046/j.1365-2265.2000.01071.x.
33. Bassett JHD, Swinhoe R, Chassande O, Samarut J, Williams GR Thyroid Hormone Regulates Heparan Sulfate Proteoglycan Expression in the Growth Plate. Endocrinology. 2006;147:295-305. https://doi.org/10.1210/en.2005-0485 PMid:16223867.
34. Gaspard T, Wondergem R, Hamamdzic M, Klitgaard HM, Serum somatomedin stimulation in thyroxine treated hypophysectomized rat. Endocrinology. 1978;102:606-11. https://doi.org/10.1210/endo-102-2-606 PMid:743982.
35. Burstein P, Draznin B, Johnson CJ, Schalch DS. The effects of hypothyroidism on growth, serum growth hormone, the growth hormone dependent somatomedin, insulin-like growth factor, and its carrier protein in rats Endocrinology. 1979;104:1107-11. https://doi.org/10.1210/endo-104-4-1107 PMid:436752.
36. Ramos S, Goya L, Alvarez C, Martin-Leone MA, Pascual AM. Effect of thyroxine administration on the IGF/IGF binding protein system in neonatal and adult thyroidectomized rats. J Endocrinol. 2001;169:111-22. https://doi.org/10.1677/joe.0.1690111 PMid:11250652.
37. Akin F, Yaylali GF, Turgut S, Kaptanoglu B. Growth hormone/insulin-like growth factor axis in patients with subclinical thyroid dysfunction. Growth Horm IGF Res. 2009;19:252-5. https://doi.org/10.1016/j.ghir.2008.11.003 PMid:19111490.
38. Soliman AT, Omar M, El Awwa A, Rizk MA, El Alaily R, Bedair EMA. Linear Growth, Growth-Hormone Secretion and Igf-I Generation in Children With Neglected Hypothyroidism Before And After Thyroxine Replacement. J Trop Ped. 2008;54:347-9. https://doi.org/10.1093/tropej/fmn030 PMid:18450819.
39. Nato-Salonen K, Muller HL, Hoffman AR, Vu TH, Rosenfeld RG. Mechanisms of thyroid hormone action on the insulin-like growth factor system: all thyroid hormone effects are not growth hormone mediated. Endocrinology. 1993;132:781-8. https://doi.org/10.1210/en.132.2.781 https://doi.org/10.1210/endo.132.2.7678799 PMid:7678799.

ABOUT AUTHORS

Elizabeth O. Johnson
Professor of Anatomy, National & Kapodistrian University of Athens, School of Medicine Laboratory for Education & Research in Neuroscience

She was previously Associate Professor of Anatomy-Histology-Embryology at Ioannina University and research associate at the National Institutes of Health (NIH). She as served as Visiting Professor at various universities in Europe and the USA. She had a joint position at the National Institute of Child Health and Human Development and National Institute of Mental Health. Johnson was trained in Functional Neuroanatomy & Neurobiology at Cornell University, Functional Neuroanatomy &Psychoneuroendocrinology at the University of Maryland, and post-doctoral training in Molecular Neuroendocrinology & Chemical Neuroanatomy at the NIH. Johnson has focused her research in areas related to chemical, molecular and functional neuroanatomy. She has extensively studied in the neuroendocrine alterations associated with stress, including the hypothalamic-pituitary-adrenal axis and glucocorticoid signaling, in both clinical and basic science research projects. The bulk of her studies are marked by both a multi-level (in-vivo, in-situ and in-vitro), as well as a multi-disciplinary approach aimed at addressing the structure and function of the nervous system. Johnson's scientific record lists over 250 scientific contributions to the international scientific literature where here published original work as amassed over 5,000 citations. She is on the Editorial Board of core anatomical textbooks and atlases, such as Grey's Anatomy for Students, and has written her own textbook on Neuroanatomy. As a result of her experimental studies, she has actively presented in over 180 scientific meetings, with more than 130 invited lectures at meetings and seminars. She serves on several expert panels as Scientific Peer Reviewer, is a member of over 10 Editorial Boards, and a Reviewer in over 35 journals.

Dimitrios Mytilinaios MD, PhD

Dimitrios Mytilinaios is a board certified Forensic Pathologist and he is the Head of the Laboratory of Forensic Medicine of the Hellenic Air Force Hospital. He is also Content Manager at Kenhub GmbH, an online e-larning platform for anatomy and histology. He holds a PhD in human neuroanatomy and his main interests are the microscopic anatomy of human hypothalamus and the use of online tools for medical education. He has published many research papers in peer-reviewed journals in the field of neuroanatomy and neuroapathology.

Eleni Nikolopoulou, PhD Candidate
National & Kapodistrian University of Athens, School of Medicine, Laboratory for Education & Research in Neuroscience

Nikolopoulou has a Bachelors and Masters in Molecular Biology with focus on:"Expression Analysis of specific ribonucleases in different neoplasias" and "Characterization of alternative mechanisms of telomere maintenance in glioma stem cells", respectively. Her current research focuses on the role of glucocorticoid receptors in the stress response and stress-related disorders. Her work has already accumulated publications in international journals.

Antonia Charchanti, Assistant Professor of Anatomy-Histology-Embryology, University of Ioannina, School of Medicine

Charchanti is a pathologist with expertise in electron microscopy. She teaches all aspects of anatomy at the University of Ioannina. Her main research focus has been on microscopic anatomy and cancer. She has numerous publications in the international literature.

Theodore Troupis, AssoicateProfessor of Anatomy
National & Kapodistrian University of Athens, School of Medicine

Troupis is a general surgeon. The scientific interest has focused on the field of clinical and surgical anatomy and includes experimental and clinical research. The bulk of studies related with medical / anatomical education sciences, surgical anatomy of abdomen, surgical anatomy of head and neck and the macro- and microanatomic brain lesions after ischemic injury. His primary research focus has resulted in numerous international publications and presentations.

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