

Thyroid Activity in Patients with Major Depression

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ABSTRACT

Hypothalamus-pituitary-thyroid (HPT) axis dysfunction has been associated with pathophysiology of major depression. The aim of the study was to determine serum levels of total 3,5,3'-triiodothyronine (T3), total thyroxine (T4) and thyroid-stimulating-hormone (TSH) in patients with major depression and healthy controls. The study included 53 medication-free patients with depression and 49 healthy controls. Exclusion criteria for patients was: other axis-I and axis-II diagnoses, intensive psychotherapy or electroconvulsive therapy, prior clinical and/or laboratory evidence of hypo- or hyperthyroidism, alcohol or nicotine dependence, pregnancy, hormone supplement therapy, somatic illnesses (diabetes, renal or hepatic disorders), infections or autoimmune diseases, recent surgical treatment or significantly changed body weight. For controls: the presence of psychiatric disorders and/or thyroid dysfunctions. The diagnosis of major depression was made using structured clinical interview based on DSM-IV criteria. The results showed significantly lower T3 and TSH levels in patients compared to controls. There was no significant difference in T4 values between patients with depression and control subjects. The results showing altered levels of thyroid hormones in depression indicate that further research on thyroid hormone activity can contribute to the better understanding of the biological basis of depression. Based on the high frequency of the subtle neuroendocrine disorders coexisting with depression, the association of thyroid abnormalities and depression should not be underestimated. Future research should identify different behavioral endophenotypes characteristic for depression, which would greatly facilitate delineating the biological phenomena associated with this psychiatric illness.

Key words: thyroid, T3, T4, TSH, major depression

Introduction

Thyroid hormones (3,5,3'-triiodothyronine /T3/, thyroxine /T4/ and thyroid-stimulating-hormone /TSH/) regulate development, metabolism and function of many organs. They exert a multitude effects on the central nervous system including modulation of gene expression¹, action on membrane-bound receptors and second-messengers², neurotransmission³ and promotion of the neurogenesis in adult brain⁴. Based on the results of the selective uptake of the labeled T3 in synaptosomes, and localization of specific T3 receptors on the synaptic membrane, it has been postulated that T3 could act as a neurotransmitter in the brain⁵.

Numerous multidisciplinary studies documented a high prevalence of mood disorders, and particularly depression, among patients with thyroid dysfunction. Although the role of T3, T4 and TSH in the pathophysio-

logy of mental disorders is not clear, it has been suggested that small changes of thyroid hormone levels, even within the normal range, might be related with the altered brain function in depression⁶, schizophrenia⁷, and posttraumatic stress disorder⁸. There is a strong possibility that the etiology and treatment outcome of depression could be related to the thyroid status. Literature data on the plasma hormone values in patients with depression are controversial. An increase⁹ and a decrease¹⁰ in plasma TSH levels, a decrease in T3¹¹ or both T3 and TSH¹² or increase in T4 and TSH with no change in T3 levels¹³ were observed in patients with depression compared to healthy controls.

In order to contribute to the better understanding of the relationship between thyroid activity and depression, we conducted a preliminary study in which we assessed

the thyroid function by measuring serum total T3, total T4 and TSH levels in patients with major depression with no prior history of thyroid-related illnesses and in healthy controls.

Methods

The study included 43 (30 female, 13 male) nonsuicidal and nonpsychotic patients with depression (mean age \pm SD, 48 ± 11.9 years). The diagnosis of major depression was made using structured clinical interview based on DSM-IV criteria¹⁴. All patients had a minimum total score of 21 on the Montgomery-Asberg Depression Rating Scale¹⁵. Patients were in stable medical condition. Exclusion criteria were: other axis-I and axis-II diagnoses, intensive psychotherapy or electroconvulsive therapy, prior clinical and/or laboratory evidence of hypo- or hyperthyroidism, alcohol or nicotine dependence, somatic illnesses (diabetes, renal or hepatic disorders), infections or autoimmune diseases, recent surgical treatment or significantly changed body weight. Pregnant or lactating female subjects or those taking estrogen therapy and contraceptives were not included in the study. Control group consisted of 59 (41 female, 18 male) healthy control subjects (mean age 52 ± 8.0 years) with no psychiatric disorders and thyroid dysfunctions. All subjects were medication free for at least 8 days prior to blood sampling. Written informed consent was obtained from all participants. The study was approved by the Local Ethics Committee and was performed in accordance with Declaration of Helsinki.

Blood sampling was always done at 8:00 a.m. (to avoid the influence of circadian rhythm), after an overnight fasting. In patients blood samples were taken before their admission at hospital. Serum levels of total T3, total T4 and TSH were determined with commercially available radioimmunoassay (RIA) kits and time-resolved fluoroimmunoassay (Delfia) with the kits from Perkin-Elmer, USA. The normality ranges were as follows: T3: 1.3–2.5 nmol/L; T4: 69–145 nmol/L; TSH: 0.3–4.0 mU/L. Intra- and inter-assay variation coefficients were 2.5% for T3, 3.6% for T4 and 3.5% for TSH.

Data are presented as mean \pm SD. Statistical evaluation of the data (means \pm SD) was done using Mann-Whitney test. All calculations were made using statistical program SigmaStat (Jandel, version 3.1, Jandel, USA)

Results

A significant difference in T3 and TSH levels was observed among groups (Figure 1). Patients with depression had significantly lower T3 ($T_{43,59}=331.0$, $P=0.026$, Mann-Whitney test) and TSH ($T_{43,59}=1772.0$, $P=0.004$, Mann-Whitney test) levels than healthy controls. There was no significant ($T_{43,59}=221.5$, $P=0.847$, Mann-Whitney test) difference in T4 values between patients with depression (111.2 ± 27.8 nmol/L) and controls (112.6 ± 19.1 nmol/L). Although altered (T3, TSH) and unaltered (T4) hormone values were observed in patients as com-

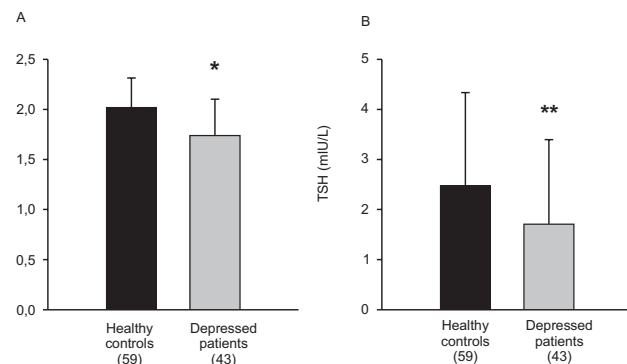


Fig. 1. (A) Serum levels of the T3 and (B) serum levels of the TSH in depressed patients and healthy controls. Each column represents mean \pm SD. Number of subjects is given in parenthesis. * $P=0.026$ vs. healthy controls; ** $P=0.004$ vs. healthy controls (Mann-Whitney test).

pared to healthy controls, mean hormone values in both groups were within the normal range.

Discussion

The results of the present study confirm the presumption that major depression might be associated with altered levels of thyroid hormones. Our results of lower total T3 and TSH levels in patients with depression are in agreement with previous data^{10,12}, but are in contrast with the reports of the unaltered or increased secretion of thyroid hormones in patients with depression⁹. The difference between studies might be due to a small number of participants and inadequate exclusion criteria. Various factors influence thyroid hormone levels like stress, malnutrition, smoking, circadian variation, sleep deprivation, alcoholism, pregnancy, aging, thyroid medications, other medications (lithium, corticosteroids, phenytoin, salicylates, furosemide, propranolol, amiodarone) and concomitant clinical disease, which greatly complicates the designs of the possible studies with thyroid hormones.

Although depression is clearly not caused by the thyroid dysfunction and patients are generally viewed as euthyroid, many patients with depression show subtle alterations in thyroid function as a consequence of altered hypothalamus-pituitary-thyroid axis (HPT) activity¹⁶. Results of our study, showing lower T3 and TSH (but still within normal range) in patients with depression, resemble euthyroid sick syndrome, related to abnormalities in thyroid function occurring often in patients with non-thyroidal illnesses¹⁷. It is manifested with normal, low or high serum TSH occurring in conjunction with normal or low total T4 and low total T3 levels, that generally return to normal values with successful treatment of the primary disease.

The alterations in thyroid function in depression might be due to decreased T4 to T3 conversion, alterations in serum thyroid hormone binding proteins, decreased concentration of TSH or its effect on the thyroid.

Cytokines, free fatty acid, cortisol and glucagon have also been studied as possible mediators of thyroid function¹⁸⁻¹⁹. Sub-clinical thyroid dysfunction may constitute an expression of a coordinated neuroendocrine-immune response to nonthyroidal disorder²⁰.

The alterations in T3 levels could have an important role in the stress induced atrophy and death of neurons²¹, which is related to pathophysiology and treatment of depression. T3 promoted neurogenesis in brains of developing and mature rats²², while thyroid hormone deficiency reduced growth and the number of cells in the dentate gyrus and induced abnormal neuronal migration and maturation in adult rats²³. In addition, hypothyroid animals displayed a depressive-like behavior, suggesting that subclinical hypothyroidism may lower the threshold for the occurrence of depression²⁴.

In clinical trials, co-administration of T3 with antidepressants improved the treatment response in major²⁵ and non-refractory depression²⁶. Pathophysiology of depression is associated with a higher sensitivity of beta-adrenergic receptors, inhibition of the deiodinase, and concomitant decrease in brain T3 and serotonin levels²⁷. Mode of action of various antidepressants including selective serotonin reuptake inhibitors (SSRIs) involves the stimulation of type II deiodinase in the rat brain, with no effect on type III deiodinase²⁸. These effects lead to the increased cerebral T3 concentrations and increased serotonergic neurotransmission. Recently, Lifschytz et al.²⁹ found also that T3, alone and in combination with the SSRI fluoxetine, reduced mRNA transcription for the somatodendritic 5-HT1A and nerve terminal 5-HT1B autoreceptors.

Alterations in the HPT axis in non-treated depression could be related and/or partially explained by serotonin and/or noradrenalin brain alterations in depression. The

role of T3 in serotonergic and the noradrenergic systems has been acknowledged, thus confirming the close relation between the thyroid activity and depressive disorders. Current models of etiology of depression propose that reduced hippocampal neurogenesis is likely associated with excess adrenal steroid and cytokine secretion, with consequent reductions in neurotrophic factors, such as brain derived neurotrophic factor (BDNF)³⁰.

Conclusions

Since thyroid hormones are important regulators of HPT axis, and many of their complex actions have been demonstrated, like interactions with neurotransmitters, enhancement of neuronal plasticity, stimulation of hippocampal neurogenesis, and influence on the expression of various neurotrophins including BDNF^{4,31}, further research on thyroid hormone activity can contribute to the better understanding of the biological basis of depression. Moreover, based on the high frequency of the subtle neuroendocrine disorders and, coexisting with depression, the association of thyroid abnormalities and depression should not be underestimated. With the use of thyroid function tests, future research should identify different behavioral endophenotypes characteristic for depression, which would greatly facilitate delineating the biological phenomena associated with this psychiatric illness.

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REFERENCES

- VIQUERIE N, LANGIN D. *Curr Opin in Clin Nutr Metab Care*, 6 (2003) 377. — 2. NEWMAN M, AGID O, GUR E, LERER B. *Int J Neuropsychopharmacol*, 3 (2003)187. — 3. SANDRINI M, VITALE G, VERGONI AV, OTTANI A, BERTOLINI A. *Life Sci*, 58 (1996) 1551. — 4. AMBROGINI P, CUPPINI R, FERRI P, MANCINI C, CIARONI S, VOICI A, GERDONI E, GALLO G. *Neuroendocrinol*, 81 (2005) 244. — 5. DRATMAN MB, GORDON JT. *Thyroid*, 6 (1996) 639. — 6. BAHLS SC, DE CARVALHO GA. *Rev Bras Psiquiatr*, 26 (2004) 40. — 7. YAZICI K, YAZICI AE, TANELI B. *Prog Neuropsychopharmacol Biol Psychiat*, 26 (2002) 579. — 8. KARLOVIC D, KOZARIC-KOVACIC D, KOCLJAN HERCIGONJA D. *Military Medicine*, 10 (2002) 846. — 9. BERLIN I, PAYAN C, CORRUBLE E, PUECH AJ. *Int J Neuropsychopharmacol*, 2 (1999) 105. — 10. RAO ML, RUHRMANN S, RETEY B, LIAPPIS N, FUGER J, KRAEMER M. *Pharmacopsychiat*, 29 (1996) 180. — 11. SAGUD M, PIVAC N, MUCK-SELER D, JAKOVLJEVIC M, MIHALJEVIC-PELES A, KORSIC M. *Neuropsychobiol*, 45 (2002)139. — 12. RUPPRECHT R, RUPPRECHT C, RUPPRECHT M, NODER M, MAHLSTEDT J. *Biol Psychiat*, 25 (1989) 22. — 13. KIRKEGAARD C, KORNER A, FABER J. *Biol Psychiat*, 27 (1990) 472. — 14. AMERICAN PSYCHIATRIC ASSOCIATION DIAGNOSTIC AND STATISTICAL MANUAL OF MENTAL DISORDERS, 4TH ED, (American Psychiatric Press, Washington DC, 1994). — 15. MONTGOMERY SA, ASBERG M. *A Br J Psychiat*, 134 (1979) 382. — 16. FOUNTOULAKIS KN, KANTARTZIS S, SIAMOULI M, PANAGIOTIDIS P, KAPRINIS S, IACOVIDES A, KAPRINIS G, IACOVIDES A, KAPRINIS G. *World J Biol Psychiat*, 7 (2006) 131. — 17. BERMUDEZ F, SURK M, OPPENHEIMER J. *J Clin Endocrinol Metabol*, 41 (1975) 27. — 18. BAUMGARTNER A, RIEMANN D, BERGER M. *Biol Psychiat*, 28 (1990) 567. — 19. MOORADIAN AD, REED RL, OSTERWEIL D, SCHIFFMAN R, SCUDER P. *J Clin Endocrinol Metabol*, 71 (1990) 1239. — 20. MAES M, SCHARPE S, COSYNS P, MELTZER H. *J Psychiat Res*, 28 (1994)123. — 21. DUMAN RS. *Biol Psychiatry*, 56 (2004)140. — 22. MARTINEZ R, GOMES FC. *J Neurosci Res*, 80 (2005) 341. — 23. MONTERO-PEDRAZUELA A, VENERO C, LAVADO-AUTRIC R, FERNANDEZ-LAMO I, GARCIA-VERDUGO JM, BERNAL J. *Mol Psychiat*, 11 (2006)361. — 24. HAGGERTY J, STERN R, MASON G, BECKWITH J, MOREY C, PRANGE A. *Am J Psychiat*, 150 (1993) 508. — 25. IOSIFESCU D, NIERENBERG A, MISCHOULON D, PERLIS R, PAPAPOSTAS G, RYAN JL, ALPERT JE, FAVA M. *J Clin Psychiat*, 66 (2005) 1038. — 26. ATSHULER LL, BAUER M, FRY MA, GITLIN MJ, MINTZ J, SZUBA MP. *Am J Psychiat*, 158 (2001) 1617. — 27. NEMEROFF CB. *J Clin Psychiat*, 50 (1989) 13. — 28. ERAVCI M, PINNA G, MEINHOLD H, BAUMGARTNER A. *Endocrinology*, 141 (2000) 1027. — 29. LIFSCHYTZ T, SEGMAN R, SHALOM G, LERER B, GUR E, GOLZER T, NEWMAN ME. *Current Drug Targets*, 7 (2006) 203. — 30. JOFFE RT. *J Psychiat Neurosci*, 31 (2006) 367. — 31. DESOUSA LA, LADIWALA U, DANIEL SM, AGASHE S, VAIDYA RA, VAIDYA VA. *Brain Res Bull*, 44 (2005) 549.

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NASLOV HRV????????????????????

S A Ž E T A K

Patofiziologija depresije se povezuje između ostaloga i s poremećenom funkcijom osovine hipotalamus-hipofiza-štitna žlijezda. Cilj ovog istraživanja bio je odrediti koncentraciju hormona štitnjače: ukupnog trijodtironina (T3), ukupnog tiroksina (T4) i tireotropin-stimulirajućeg-hormona (TSH) u bolesnika s velikim depresivnim poremećajem i usporediti ih s vrijednostima u zdravih osoba. Ispitanici su bili 53 bolesnika s depresijom i 49 zdravih osoba, starijih od 18 godina. Dijagnoza velikog depresivnog poremećaja je postavljena primjenom strukturiranog kliničkog intervjua prema DSM-IV kriterijima. Bolesnici su imali najmanje 21 bod na Montgomery-Asberg ocjenskoj ljestvici za depresiju. U kontrolnu skupinu ispitanika uključene su zdrave osobe, koje nisu uzimale lijekove, te koje u obitelji nemaju duševnih bolesnika. Iz istraživanja su isključene osobe kod kojih je bila prisutna zlouporaba psihoaktivnih tvari i alkohola, osobe sa somatskim bolestima (dijabetes, bolesti bubrega, jetre), i osobe čiji prethodni klinički ili laboratorijski nalazi upućuju na hipo ili hipertireozu. Rezultati su pokazali statistički značajno sniženu koncentraciju T3 i TSH u bolesnika u usporedbi s vrijednostima hormona štitnjače u zdravih osoba. Koncentracija T4 bila je podjednaka u depresivnih bolesnika i zdravih osoba. Rezultati upućuju na promjene koncentracija hormona štitnjače u depresivnih bolesnika, koje ne bi trebalo zanemariti. Nastavak istraživanja različitih endofenotipova karakterističnih za depresivni poremećaj trebao bi pridonijeti razjašnjenju etiologije i biološke podloge depresije.