Platelet serotonin concentration and monoamine oxidase activity in hypothyroid patients

Stipčević, Tamara; Kusačić-Kuna, Sanja; Deželjin, Martina; Dodig, Damir; Koršić, Mirko; Pivac, Nela; Mück-Šeler, Dorotea

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Title: Platelet serotonin concentration and monoamine oxidase activity in hypothyroid patients

Authors: Stipcevic Tamara[a] Kusacic-Kuna Sanja[b] Dezeljin Martina[a] Dodig Damir[b] Korsic Mirko[c] Pivac Nela[a] Muck-Seler Dorotea[a]

Affiliation:

[a]Division of Molecular Medicine, Rudjer Boskovic Institute, Zagreb, Croatia

[b]Department of Nuclear Medicine and Radiation Protection, University Hospital Center, Zagreb, Croatia

[c]Department of Endocrinology, University Hospital Center, Zagreb, Croatia

Running title: Platelet 5-HT and MAO B in hypothyroidism

- Established facts: Female hypothyroid patients had significantly lower platelet serotonin concentrations, similar platelet monoamine oxidase type B activity, significantly higher TSH levels, and significantly lower T4 levels than euthyroid healthy women.
- Novel insights: The new findings of the present study were decreased platelet serotonin concentrations, and the lack of any significant correlations between platelet biochemical markers and thyroid hormones. These results suggest that hypothyroid patients have an altered interaction between serotonergic system and hypothalamic-pituitary-thyroid axis activity.

Abstract

Background/Aim: The relationship between hypothalamic-pituitary-thyroid (HPT) axis and serotonergic (5-HT) system is not clear. The aim of the study was to determine platelet biochemical markers (5-HT concentration and monoamine oxidase /MAO-B/ activity) in hypothyroid patients.

Methods: The study included 25 female medication-free hypothyroid patients in postoperative follow-up after total thyroidectomy due to papillary thyroid carcinoma, who were not treated with synthetic thyroxine (T4) for 4 weeks, and 44 age matched euthyroid healthy women. Platelet 5-HT concentration, platelet MAO-B activity, total T4 and thyroid stimulating hormone (TSH) levels were determined using spectrofluorimetric methods, radioimmunoassay and fluoroimmunoassay, respectively.

Results: Hypothyroid patients had significantly higher TSH, significantly lower T4 levels and platelet 5-HT concentration, and unchanged platelet MAO-B acrivity than healthy subjects. A positive correlation between 5-HT concentration and platelet MAO-B activity, and between platelet MAO-B activity and T4 in control subjects was found.

Conclusions: Reduced platelet 5-HT concentrations in hypothyroid patients suggests a complex interaction between 5-HT system and HPT axis activity, which could be related to frequent occurrence of depressive symptoms in hypothyroid patients. The determination of platelet 5-HT concentration should be considered as a diagnostic tool for the evaluation of depressive symptoms in hypothyroid patients during hormone withdrawal procedure.

Key words: Platelet 5-HT● Platelet MAO B ● hypothyroidism ●thyroxine ● thyroid stimulating hormone

Introduction

Hormones of the hypothalamic-pituitary-thyroid (HPT) axis: triiodothyronine (T3), thyroxine (T4), and thyroid stimulating hormone (TSH), play an important role in the development of the central nervous system [1], regulate the metabolism and function of various neurotransmitters [2-4], their receptors, second-messengers [5], and gene expression [6]. Evidence for the interaction between serotonin (5-hydroxytryptamine, 5-HT) and thyroid hormones originates mostly from the experimentally-induced hypothyroid state in animals [3]. Decreased 5-HT [7,8] and increased 5-hydroxyinoleacetic acid [9] concentrations were observed in neonatal and adult hypothyroid rats, suggesting an increased 5-HT turnover [7,10], while T3 administration to hypothyroid animals normalized 5-HT turnover to normal values [10].

The relationship between HPT axis and 5-HT system in humans are scarce and focused on alterations of thyroid hormones in psychiatric patients. Hypothyroidism appears in 8% of adult population [11], and could be one of the risk factors for the development of depression [12]. The augmentation therapy with T3 or T4 to different antidepressants induced remission in treatment resistant depressed patients [13]. In hypothyroid female patients, the treatment with T4 induced a significant decrease in pretreatment values of 5-HT and catecholamine precursor in cerebrospinal fluid [14]. A significant decrease in D-fenfluramine-induced cortisol response was also found in hypothyroid patients [15], probably due to a decrease in 5-HT2A receptor sensitivity [16]. It has been hypothesized that alterations in HPT axis in non-treated depressions, could be explained by both 5-HT and noradrenalin (NE) brain alterations [17]. In particular NE participates in the release of TRH (thyrotrophin releasing hormone) and TSH [18]. In hypothyroidism deficiency of T3 accompanied by increase in TSH in the brain alters the noradrenergic neurotransmission by reducing beta-adrenergic receptors [19]. Additional studies on TSH are scarce and inconsistent in depressed patients. Excessive response of TSH to the TRH challenge test has been found in 10% [20] and decreased response in 25% of the patients [21].

Blood platelets are considered to be a limited peripheral model for the central 5-HT neurons due to similarities in the structure and function of 5-HT receptors and 5-HT transporter, expressed both in platelets and 5-HT neurons [22], while platelet biochemical markers (5-HT concentration, monoamine oxidase type B (MAO-B) activity) might be used

as peripheral biological and/or trait markers for particular symptoms in depression [23,24] or schizophrenia [25,26]. Platelet 5-HT originates from the peripheral pool of 5-HT which is synthesized in the enterochromaffin cells of the gastrointestinal tract, released via blood stream into platelets and stored in dense granules. Platelet 5-HT is involved in the thrombus formation and atherogenesis, vasoconstriction on the site of endothelial injury, has a growth factor role for mitogenesis of arterial smooth muscle cells, proliferation of endothelial cells, and in vascular inflammation, it is associated with atherogenesis by increasing the synthesis of interleukin-6 in vascular smooth muscle cell [27]. Besides these functions, platelet 5-HT acts as a neurotransmitter for the peripheral nervous system, influences gastric and intestinal ion secretion and intestinal motility [28], and plays an additional role as an enhancer of platelet aggregation [29]. The mitochondrial enzyme MAO exists in two isoforms: MAO-A and MAO-B, that differ in tissue distribution and substrate specificity. Platelets include only MAO-B isoform, which regulates the levels of exogenous, dietary amines in peripheral tissues (phenylethylamine), but it can also oxidize dopamine, noradrenaline, adrenaline, tryptamine and tyramine, and is inhibited by deprenyl [30]. When MAO-A enzyme is absent or inhibited, MAO-B metabolizes also 5-HT [31]. In hypothyroidism, some studies [32,33] found no significant differences in platelet activities between the hypothyroid patients and healthy subjects, while in a more recent study, difference in the mean platelet volume, with no changes in platelet counts, was found in patients compared to healthy controls [34].

In accordance with the relationship between HPT axis and 5-HT system, we hypothesized that platelet biochemical markers would be altered in hypothyroid patients. The aim of this study was to determine platelet 5-HT concentration and platelet MAO-B activity in medication-free female patients in hypothyroid state induced by withdrawal of levothyroxine after total thyroidectomy due to papillary carcinoma and in age and sex matched euthyroid healthy control subjects.

Patients and Methods

The study included 25 female patients (mean age 49.3 ±1.2 years; range 24-74 years) who had undergone total thyroidectomy due to papillary carcinoma. The average time since thyroidectomy was 3.4 ± 1.8 years. All patients were currently in hypothyroid state with elevated TSH after withdrawal of replacement T4 (levothyroxine) therapy during 4 weeks, but in good health and without post-operative complications such as hypoparathyroidism or cancer recurrence. Hypothyroid state was required to increase sensitivity of serum

thyroglobulin test (>2 µg/L) and radioiodine whole-body scanning (which showed no pathological activity) in the evaluation the effectiveness of surgical treatment [35]. Control group consisted of 44 female euthyroid healthy subjects (mean age 46.2 ± 8.9 years; range 28-77 years). Control subjects with abnormal liver or thyroid function tests were excluded. Apart of radiological and nuclear medicine testing, control subjects were examined in the same manner as patients. Twelve patients and 17 healthy controls were in menopause. All subjects were nonsmokers and free of concomitant psychiatric and additional endocrine illnesses. Subjects taking antihypertensive, antiallergic, anxiolytic, antirheumatic, cholesterol lowering, hormonal supplemental or contraceptive therapy and drugs affecting platelet 5-HT values (antidepressants) or MAO-B activity (MAO inhibitors) were excluded from the study. The study was approved by Local Ethics Committee and all participants gave their written informed consent.

Each patient underwent a complete medical evaluation before radiological examination and blood sampling. After an overnight fasting and between 8 and 10 am, 5 ml of blood was drawn from cubital vein into tube for the analysis of serum T4 and TSH levels. Additional 5 ml of blood was taken in tube containing 1 ml of acid citrate dextrose anticoagulant for the determination of platelet 5-HT concentration and platelet MAO-B activity. Platelet-rich plasma (PRP) was obtained by centrifugation (935×*g*) for 70 s at room temperature. Platelets were sedimented by further centrifugation of PRP at 10 000×*g* for 5 min. The platelet pellet was washed with saline and centrifuged again. Platelet 5-HT concentrations and platelet MAO-B activity were determined by the spectrofluorimetric methods, as previously described [36] using Varian Carry Eclypse spectrofluorimeter. Platelet protein was determined by the method of Lowry et al. (1951). [37]

Serum T4 and TSH were determined by a radioimmunoassay (RIA) and time-resolved fluoroimmunoassay (Delfia) with the kits from Perkin-Elmer. Intra and inter assay variation coefficients were 3.6% for T4 and 3.5% for TSH. The range of normal values was 70-165 nmol/l for T4 and 0.4-4.2 mU/l for TSH.

The results are expressed as mean ± standard deviations (S.D.). The differences between groups were evaluated by Mann Whitney t-test. The correlation between parameters was determined using Spearman's coefficient of correlation. The criterion for significance in all test was $P<0.05$. The statistical package used was SigmaStat 3.1.

Results

As expected, TSH values were significantly (P<0.001) higher, and T4 significantly (P<0.001) lower in hypothyroid patients compared to hormone values in healthy subjects (Table 1). Platelet MAO-B activity did not differ significantly (P=0.120) between patients and control subjects (Table 1).

Platelet 5-HT concentration differed significantly (P<0.001) between patients and healthy controls (Figure 1), and 5-HT values were significantly, i.e. 35% lower in hypothyroid patients than in euthyroid control subjects.

A significant positive correlation between 5-HT levels and platelet MAO-B activity was found in control subjects (r=0.581; P=0.000), but not in hypothyroid patients (r=0.372; P=0.067). No significant correlation was observed between platelet 5-HT and T4 levels in healthy subjects (r=0.249; P=0.103) or in patients (r=0.115; P=0.579), or between platelet 5-HT and TSH levels in healthy subjects (r=-0,276; P=0.070) or in patients (r=0.244; P=0.237). There was a significant positive correlation between platelet MAO activity and T4 levels in healthy controls (r=0.322; P=0.033), but not in patients (r=-0.067; P=0.75). No significant correlation was observed between platelet MAO activity and TSH levels in healthy subjects (r=0.004; P=0.98) or in patients (r=0.131; P=0.529).

Discussion

The main finding of the present study was that subjects in pronounced hypothyroid state, induced by withdrawal of replacement T4 therapy after thyroidectomy, had significantly lower platelet 5-HT concentrations than euthyroid control subjects. This is the first study showing reduced platelet 5-HT concentration in hypothyroid patients, and these data suggest that hypothyroidism influences peripheral i.e. platelet 5-HT system.

A reduced platelet 5-HT concentration is associated to female gender, comorbid diagnosis, alcoholism, suicidal behaviour, or antidepressant treatment. The effect of sex [23, 24,25,26,38] was excluded in this study, since we recruited only female subjects. The effects of comorbid diagnosis [38], suicidal behaviour [23,24,25], alcoholism [39], or the effects of different medications [24, 36] were ruled out by the study exclusion criteria. To avoid the influence of the daylight exposure on platelet 5-HT values [40] patients and controls were sampled at the same time. Different phases of the menstrual status might influence platelet 5-

HT concentrations, platelet MAO-B activity and serum T4 and TSH values. However, no significant differences in whole blood 5-HT [41], serum T3 and T4 [42] levels were detected in healthy women during follicular, ovulatory or luteal phases of the menstrual cycle. Although a positive correlation between platelet 5-HT concentration and plasma estrogen levels was found [43], we have shown similar platelet 5-HT concentration between premenopausal and postmenopausal healthy, depressed and schizophrenic women [44]. Our results showed that platelet 5-HT concentrations were reduced in hypothyroid patients, and these data might be in line with hypothyroidism-induced reduction of central 5-HT activity, since reduced responses to both cortisol and prolactin (index of central 5-HT responsivity) to d-fenfluramine (centrally acting 5-HT releasing agent) were found in hypothyroid patients [15].

The decrease in platelet 5-HT concentration in the present study suggests a reduced 5-HT synthesis or increased metabolism. Preclinical data showed a decreased activity of the tryptophan hydroxylase, a rate limiting enzyme involved in the biosynthesis of 5-HT, in animals with experimentally induced hypothyroidism [7].

The reduced platelet 5-HT concentration from our study could be related to the increased metabolism of 5-HT, due to the altered activity of MAO in patients with severe hypothyroidism. However, female hypothyroid patients and control subjects had similar platelet MAO-B activity (present study), and MAO-B activity was not affected by thyroid hormones in the rat brain [45], indicating that thyroid hormone status did not alter significantly platelet MAO-B activity. Platelet MAO-B activity might be affected by various factors such as gender, age, ethnicity, smoking, some neurodegenerative diseases, medication [46], and to control for these variables, the present study included only medication-free female Caucasian patients with no neurodegenerative diseases matched for age with control subjects, and all participants were nonsmokers. Even though 5-HT is not a main substrate for MAO-B [46], since MAO-A preferentially metabolizes 5-HT, it has been shown that MAO-B could be involved in the direct regulation of 5-HT synthesis in the rat brain [47] and platelet MAO-B activity has been proposed to be an indicator of the central 5-HT system [46]. Preclinical studies suggest that brain and thyroid and thyroid MAO-A activity was slightly increased in hypothyroid rats. [45]. Since we did not determine MAO-A activity in our hypothyroid patients and control subjects, and there are no literature data regarding peripheral MAO-A activity in hypothyroid patients, we could only speculate that decreased 5-HT in patients with hypothyroidism might have been induced with an increased MAO-A activity.

We have found a positive correlation between platelet 5-HT concentration and platelet MAO-B activity and between T4 levels and platelet MAO-B activity in control participants, whose thyroid hormonal status and platelet biochemical markers were within the normal range. The lack of correlation between platelet 5-HT, MAO-B activity and T4 levels in patients with severe hypothyroid state suggests an altered and more complex relationship between HPT axis and 5-HT, which might be due to the reduced T4 and platelet 5-HT concentrations.

If platelet 5-HT concentration might be used as a limited peripheral indicator of the central 5-HT function [22,24,26] the results from the present study indicate that hypothyroid patients have lower platelet 5-HT concentration and possibly reduced central 5-HT function. Hypothyroid patients frequently experience depressive symptoms [48], and depressive patients [23,24], similarly to our hypothyroid patients, have decreased platelet 5-HT concentration. In addition, the addition of T3 or T4 to antidepressant therapy improved the clinical state in treatment resistant depressed patients [13]. Our results are in line with the significantly lower platelet 5-HT concentration in medication-free depressed patients compared to healthy controls [23,24]. The limitation of the present study was that patients were not evaluated with the scales or questionnaires for the presence of depressive symptoms. Our biochemical findings raise a question about a duration of withdrawal of T4 replacement therapy. Namely, withdrawal of 4 weeks duration might have severe consequences on medical status of the patients, as it has been shown that total thyroidectomy is associated with higher psychiatric morbidity than partial thyroidectomy [49]. In addition, preclinical studies showed that as early as 7 and 20 days following thyroidectomy neuronal proliferative capacity [50] and synaptic 5-HT levels [51] are reduced. To prevent a possible neuronal damage caused by 4 weeks of severe hypothyreosis [50], we and others [48] propose a reduction of the duration of T4 withdrawal from 4 weeks to 3 weeks, and/or reduction of T4 replacement dosage to half the usual amount instead of the complete withdrawal in patients preparing for scintiscanning.

In conclusion, hypothyroid patients had decreased platelet 5-HT concentrations, similar platelet MAO-B activity, higher TSH and lower T4 levels than euthyroid healthy subjects. There were no significant correlations between platelet biochemical markers and thyroid hormones in hypothyroid patinets, suggesting that hypothyroid patients have an altered interaction between 5-HT system and HPT axis activity, presumably mediated by the reduced 5-HT-induced regulation of the HPT axis activity. Our results also indicate that the use of routine peripheral 5-HT measurements (a few times during the hormone withdrawal

procedure) might be a diagnostic tool for evaluation of depressive symptoms in hypothyroid patients.

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FIGURE LEGENDS

Figure 1. Platelet serotonin (5-HT) concentrations in hypothyroid patients an euthyroid control subjects. Each column represents mean ± SD. Number of subjects is given in parenthesis. *P<0.001 vs. healthy controls (Mann-Whitney t-test).

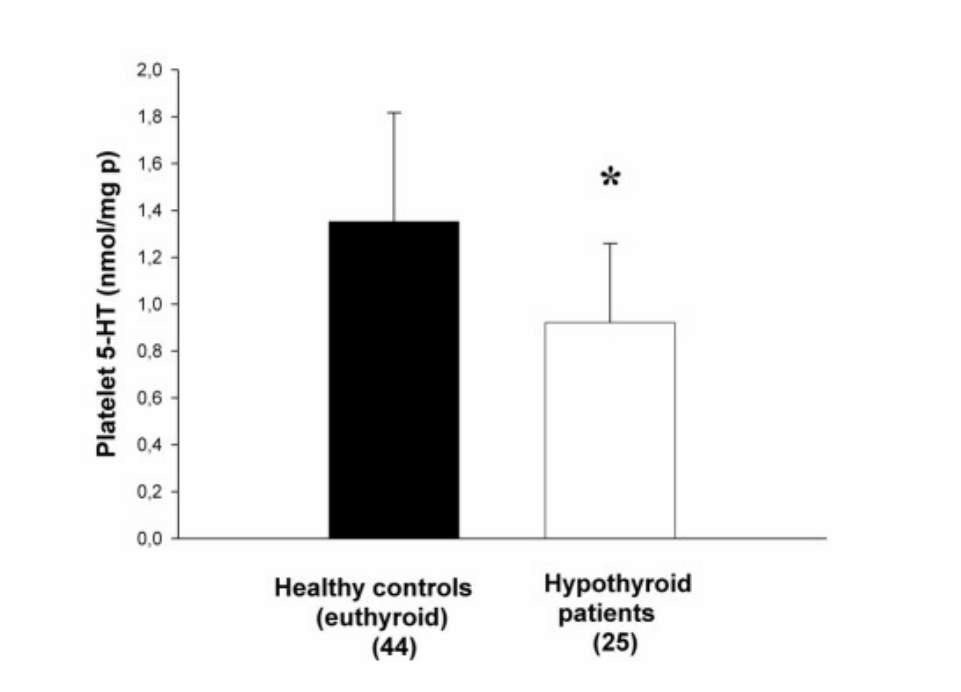

Table 1. Thyroxine (T4) and thyroid stimulating hormone (TSH) levels in euthyroid healthy controls and hypothyroid patients. Results are expressed as mean ± SD. Number of subjects is given in parenthesis.

	T4 (nmol / L)	TSH (mIJ / L)	Platelet MAO (nmol4OHQ/mg p/h)
Euthyroid controls (30)	120.4 ± 20.6*	1.52 ± 0.89*	18.98 ± 12.14
Hypothyroid patients (25)	22.1 ± 8.3	92.07 ± 30.28	19.93 ± 5.72

*P<0.001 vs. euthyroid controls (Mann Whitney t-test)