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Research Article

Content of Eleven Trace Elements in Thyroid Malignant Nodules and Thyroid Tissue adjacent to Nodules

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Abstract

Background: Thyroid malignant nodules (TMNs) are the most common endocrine cancer and the fifth most frequently occurring type of malignancies. Women are at particular risk for this thyroid disease The etiology and pathogenesis of TMNs must be considered as multifactorial. The present study was performed to clarify the role of some trace elements (TEs) in the etiology of these thyroid disorders.

Methods: Thyroid tissue levels of silver (Ag), cobalt (Co), chromium (Cr), iron (Fe), mercury (Hg), iodine (I), rubidium (Rb), antimony (Sb), scandium (Sc), selenium (Se), and zinc (Zn) were prospectively evaluated in malignant tumor and thyroid tissue adjacent to tumor of 41 patients with TMNs. Measurements were performed using non-destructive instrumental neutron activation analysis. Tissue samples were divided into two portions. One was used for morphological study while the other was intended for TEs analysis. Results of the study were additionally compared with previously obtained data for the same TEs in "normal" thyroid tissue.

Results: It was observed that in malignant tissue the mass fraction of I was 25.6 times lower, whereas mass fractions of Ag, Co, Cr, Hg, and Rb were approximately 13, 1.4, 1.6, 20 and 1.7 times, respectively, higher than in normal tissues of the thyroid. In a general sense Cr, Fe, Sb, Sc, and Zn contents found in the "normal" and "adjacent" groups of thyroid tissue samples were similar. However, in the "adjacent" group mean mass fractions of Ag, Co, Hg, I, Rb, and Se were approximately 33, 1.8, 52, 1.7, 2.6, and 1.3 times, respectively, higher, than in the "normal" group. Significant reduced levels of tumor TEs in comparison with thyroid tissue adjacent to tumor were found for Ag, Hg, I, and Se. In malignant tumor Ag, Hg, I, and Se contents were approximately 2.6, 2.6, 43, and 1.5 times, respectively, lower than in "adjacent" group of tissue samples.

Conclusions: Thus, from results obtained, it was possible to conclude that the drastically reduced level of I, as well as elevated levels of Ag, Co, Cr, Hg, and Rb in cancerous tissue could possibly be explored for differential diagnosis of benign and malignant thyroid nodules.

Keywords: Thyroid; Thyroid malignant nodules; Trace elements; Neutron activation analysis

Introduction

Thyroid malignant nodules (TMNs) are the most common endocrine cancer and the fifth most frequently occurring type of malignancies [1-3]. Women are at particular risk for this thyroid disease with 22.2/100,000 individuals affected every year [2]. The incidence of TMNs has increased worldwide over the past four decades. TMNs are divided into three main histological types: differentiated (papillary and follicular thyroid cancer), undifferentiated (poorly differentiated and anaplastic thyroid cancer, and medullary thyroid cancer, arising from C cells of thyroid [3]. For over 20th century, there was the dominant opinion that TMNs is the simple consequence of iodine deficiency [4]. However, it was found that TMNs is a frequent disease even in those countries and regions where the population is never exposed to iodine shortage. Moreover, it was shown that iodine excess has severe consequences on human health and associated with the presence of TMNs [5-8]. It was also demonstrated that besides the iodine deficiency and excess many other dietary, environmental, and occupational factors are associated with the TMNs incidence [9-11]. Among these factors a disturbance of evolutionary stable input of many trace elements (TEs) in human body after industrial revolution plays a significant role in etiology of TMNs [12].

Besides iodine, many other TEs have also essential physiological functions [13]. Essential or toxic (goitrogenic, mutagenic, carcinogenic) properties of TEs depend on tissue-specific need or tolerance, respectively [13]. Excessive accumulation or an imbalance of the TEs may disturb the cell functions and may result in cellular proliferation, degeneration, death, benign or malignant transformation [13-15]. In our previous studies the complex of in vivo and in vitro nuclear analytical and related methods was developed and used for the investigation of iodine and other TEs contents in the normal and pathological thyroid [16-22]. Iodine level in the normal thyroid was investigated in relation to age, gender and some non-thyroidal diseases [23,24]. After that, variations of many TEs content with age in the thyroid of males and females were studied and age- and gender-dependence of some TEs was observed [25-41]. Furthermore, a significant difference between some TEs contents in colloid goiter, thyroiditis, and thyroid adenoma in comparison with normal thyroid was demonstrated [42-46]. To date, the etiology and pathogenesis of TMNs must be considered as multifactorial. The present study was performed to find out differences in TEs contents between the group of cancerous tissue and thyroid visually intact tissue adjacent to tumor, as well as to clarify the role of some TEs in the etiology of TMNs. Having this in mind, the aim of this exploratory study was to examine differences in the content of silver (Ag), cobalt (Co), chromium (Cr), iron (Fe), mercury (Hg), iodine (I), rubidium (Rb), antimony (Sb), scandium (Sc), selenium (Se), and zinc (Zn) in tumor and adjacent to tumor tissues of thyroids with TMNs, using a combination of non-destructive instrumental neutron activation analysis with high resolution spectrometry of short-lived radionuclides (INAA-SLR) and long-lived radionuclides (INAA-LLR), and to compare the levels of these TEs in two groups (tumor and adjacent to tumor thyroid tissues) of the cohort of TMNs samples. Moreover, for understanding a possible role of TEs in etiology and pathogenesis of TMNs results of the study were compared with previously obtained data for the same TEs in "normal" thyroid tissue [42-46].

Material and Methods

All patients with TMNs (n=41, mean age M±SD was 46±15 years, range 16-75) were hospitalized in the Head and Neck Department of the Medical Radiological Research Centre (MRRC), Obninsk. Thick-needle puncture biopsy of suspicious nodules of the thyroid was performed for every patient, to permit morphological study of thyroid tissue at these sites and to estimate their trace element contents. In all cases the diagnosis has been confirmed by clinical and morphological results obtained during studies of biopsy and resected materials. Histological conclusions for malignant tumors were: 25 papillary adenocarcinomas, 8 follicular adenocarcinomas, 7 solid carcinomas, and 1 reticulosarcoma. Tissue samples of tumor and visually intact tissue adjacent to tumor were taken from resected materials. "Normal" thyroids for the control group samples were removed at necropsy from 105 deceased (mean age 44 ± 21 years, range 2-87), who had died suddenly. The majority of deaths were due to trauma. A histological examination in the control group was used to control the age norm conformity, as well as to confirm the absence of micro-nodules and latent cancer. All studies were approved by the Ethical Committees of MRRC. All the procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments, or with comparable ethical standards. Informed consent was obtained from all individual participants included in the study. All tissue samples obtained from tumors and visually intact tissue adjacent to tumors were divided into two portions using a titanium scalpel to prevent contamination by TEs of stainless steel [47]. One was used for morphological study while the other was intended for TEs analysis. After the samples intended for TEs analysis were weighed, they were freeze-dried and homogenized [48].

To determine contents of the TEs by comparison with a known standard, biological synthetic standards (BSS) prepared from phenol-formaldehyde resins were used [49]. In addition to BSS, aliquots of commercial, chemically pure compounds were also used as standards. Ten certified reference material IAEA H-4 (animal muscle) and IAEA HH-1 (human hair) sub-samples were treated and analyzed in the same conditions that thyroid samples to estimate the precision and accuracy of results. The content of I were determined by INAA-SLR using a horizontal channel equipped with the pneumatic rabbit system of the WWR-c research nuclear reactor (Branch of Karpov Institute, Obninsk). Details of used nuclear reaction, radionuclide, gamma-energies, spectrometric unit, sample preparation, and the quality control of results were presented in our earlier publications concerning the INAA-SLR of I contents in human thyroid [27,28] and scalp hair [50]. A vertical channel of the same nuclear reactor was applied to determine the content of Ag, Co, Cr, Fe, Hg, Rb, Sb, Sc, Se, and Zn by INAA-LLR. Details of used nuclear reactions, radionuclides, gamma-energies, spectrometric unit, sample preparation and procedure of measurement were presented in our earlier publications concerning the INAA-LLR of TEs contents in human thyroid [29,30], scalp hair [50], and prostate [51,52]. A dedicated computer program for INAA-SLR and INAA-LLR mode optimization was used [53]. All thyroid samples for TEs analysis were prepared in duplicate, and mean values of TEs contents were used in final calculation. Using Microsoft Office Excel software, a summary of the statistics, including, arithmetic mean, standard deviation of mean, standard error of mean, minimum and maximum values, median, percentiles with 0.025 and 0.975 levels was calculated for TEs contents in nodular and adjacent tissue of thyroids with TMNs. Data for "normal" thyroid were taken from our previous publications [42-46]. The difference in the results between three groups of samples ("normal", "tumor", and "adjacent") was evaluated by the parametric Student's t-test and non-parametric Wilcoxon-Mann-Whitney U-test.

Results

Table 1 presents certain statistical parameters (arithmetic mean, standard deviation, standard error of mean, minimal and maximal values, median, percentiles with 0.025 and 0.975 levels) of the Ag, Co, Cr, Fe, Hg, I, Rb, Sb, Sc, Se, and Zn mass fraction in "normal", "tumor", and "adjacent" groups of thyroid tissue samples. The ratios of means and the comparison of mean values of Ag, Co, Cr, Fe, Hg, I, Rb, Sb, Sc, Se, and Zn mass fractions in pairs of sample groups such as "normal" and "tumor", "normal" and "adjacent", and also "adjacent" and "tumor" are presented in Table 2, 3, and 4, respectively.

Table 1: Some statistical parameters of Ag, Co, Cr, Fe, Hg, I, Rb, Sb, Sc, Se, and Zn mass fraction (mg/kg, dry mass basis) in normal thyroid and thyroid cancer (tumor and adjacent to tumor "intact" thyroid tissue).

Tissue	Element	Mean	SD	SEM	Min	Max	Median	P 0.025	P 0.975
Normal thyroid	Ag	0.0151	0.014	0.0016	0.0012	0.08	0.0121	0.0017	0.0454
	Co	0.0399	0.0271	0.003	0.0046	0.14	0.0327	0.0134	0.124
	Cr	0.539	0.272	0.032	0.13	1.3	0.477	0.158	1.08
	Fe	225	100	11	51	512	217	67.4	456
	Hg	0.0421	0.0358	0.0041	0.0065	0.18	0.0304	0.0091	0.15
	I	1841	1027	107	114	5061	1695	230	4232
	Rb	7.37	4.1	0.44	1.11	29.4	6.49	2.6	16.7
	Sb	0.111	0.072	0.008	0.0047	0.308	0.103	0.0117	0.28
	Sc	0.0046	0.0038	0.0008	0.0002	0.0143	0.0042	0.00035	0.0131
	Se	2.32	1.29	0.14	0.439	5.8	2.01	0.775	5.65
	Zn	97.8	42.3	4.5	8.1	221	91.7	34.8	186
Cancer (tumor)	Ag	0.193	0.215	0.041	0.0075	1.02	0.147	0.008	0.705
	Co	0.055	0.0309	0.006	0.0042	0.143	0.0497	0.0159	0.129
	Cr	0.835	0.859	0.157	0.039	3.5	0.46	0.0941	3.05
	Fe	248	173	28	55.1	880	209	62.2	678
	Hg	0.824	0.844	0.149	0.0685	3.75	0.475	0.0689	2.85
	I	71.8	62	10	2	261	62.1	2.93	192
	Rb	12.8	4.9	0.8	5.5	27.4	12.2	6.38	21.8
	Sb	0.124	0.081	0.015	0.016	0.381	0.108	0.0174	0.315
	Sc	0.0077	0.0129	0.002	0.0002	0.0565	0.0023	0.0002	0.0447
	Se	2.04	1.02	0.18	0.143	4.7	1.8	0.663	4.33
	Zn	95.1	78.9	12.6	36.5	375	67	36.7	374
Cancer (adjacent thyroid tissue)	Ag	0.503	0.45	0.103	0.079	2	0.303	0.0984	1.53
	Co	0.0707	0.0581	0.012	0.0152	0.205	0.0455	0.017	0.201
	Cr	0.556	0.468	0.094	0.0512	1.58	0.457	0.0589	1.56
	Fe	244	137	27	95.2	752	213	104	591
	Hg	2.19	1.92	0.38	0.016	7.78	1.43	0.158	6.5
	I	3183	1673	301	563	8240	2982	853	7766
	Rb	18.8	17	3.3	5	67	11.9	5.69	65.6
	Sb	0.247	0.416	0.085	0.0069	1.77	0.0634	0.0159	1.38
	Sc	0.0059	0.0134	0.003	0.0002	0.0539	0.0002	0.0002	0.0442
	Se	3.08	1.67	0.33	0.704	6.91	2.56	0.942	6.89
	Zn	111	56	11	20.4	272	110	28.8	215

M – arithmetic mean, SD – standard deviation, SEM – standard error of mean, Min – minimum value, Max – maximum value, P 0.025 – percentile with 0.025 level, P 0.975 – percentile with 0.975 level.

Table 2: Differences between mean values (M ± SEM) of Ag, Co, Cr, Fe, Hg, I, Rb, Sb, Sc, Se, and Zn mass fraction (mg/kg, dry mass basis) in normal thyroid and thyroid cancer ((tumor).

Element	Thyroid tissue				Ratio
	Normal thyroid	**Cancer (tumor)**	**Student's t-test p£**	**U-test p**	**Tumor/Normal**
Ag	0.0151±0.0016	0.193±0.041	**0.00022**	**≤0.01**	12.8
Co	0.0399±0.0030	0.0550±0.0060	**0.022**	**≤0.01**	1.38
Cr	0.539±0.032	0.835±0.157	0.073	**≤0.05**	1.55
Fe	225±11	248±28	0.445	>0.05	1.1
Hg	0.0421±0.0041	0.824±0.149	**0.000011**	**≤0.01**	19.6
I	1841±107	71.8±10.0	**0.00000000001-11**	**≤0.01**	0.039
Rb	7.37±0.44	12.8±0.8	**0.000000084**	**≤0.01**	1.74
Sb	0.111±0.008	0.124±0.015	0.422	>0.05	1.12
Sc	0.0046±0.0008	0.0077±0.0020	0.223	>0.05	1.67
Se	2.32±0.14	2.04±0.18	0.235	>0.05	0.88
Zn	97.8±4.5	95.1±5.9	0.839	>0.05	0.97

M – arithmetic mean, SEM – standard error of mean, statistically significant values are in bold.

Table 3: Differences between mean values (M±SEM) of Ag, Co, Cr, Fe, Hg, I, Rb, Sb, Sc, Se, and Zn mass fraction (mg/kg, dry mass basis) in normal thyroid and "intact" thyroid tissue adjacent to tumor.

Element	Thyroid tissue				Ratio
	Normal thyroid	**Cancer (adjacent)**	**Student's t-test p£**	**U-test p**	**Adjacent/Normal**
Ag	0.0151±0.0016	0.503±0.103	**0.00017**	**≤0.01**	33.3
Co	0.0399±0.0030	0.0707±0.0120	**0.016**	**≤0.01**	1.77
Cr	0.539±0.032	0.556±0.094	**0.86**	>0.05	1.03
Fe	225±11	244±27	0.511	>0.05	1.08
Hg	0.0421±0.0041	2.19±0.38	**0.0000093**	**≤0.01**	52
I	1841±107	3183±301	**0.00015**	**≤0.01**	1.73
Rb	7.37±0.44	18.8±3.3	**0.0023**	**≤0.01**	2.55
Sb	0.111±0.008	0.247±0.085	0.122	>0.05	2.23
Sc	0.0046±0.0008	0.0059±0.0030	0.628	>0.05	1.28
Se	2.32±0.14	3.08±0.33	**0.038**	**≤0.01**	1.33
Zn	97.8±4.5	111±11	0.281	>0.05	1.13

M – arithmetic mean, SEM – standard error of mean, statistically significant values are in bold.

Table 4: Differences between mean values (M±SEM) of Ag, Co, Cr, Fe, Hg, I, Rb, Sb, Sc, Se, and Zn mass fraction (mg/kg, dry mass basis) in thyroid cancer and "intact" thyroid tissue adjacent to tumor.

Element	Thyroid tissue				Ratio
	Cancer (adjacent)	**Cancer (tumor)**	**Student's t-test p£**	**U-test p**	**Adjacent/Tumor**
Ag	0.503±0.103	0.193±0.041	**0.01**	**≤0.01**	0.38
Co	0.0707±0.0120	0.0550±0.0060	0.233	>0.05	0.78
Cr	0.556±0.094	0.835±0.157	0.133	>0.05	1.5

Fe	244±27	248±28	0.916	>0.05	1.02
Hg	2.19±0.38	0.824±0.149	**0.0023**	**≤0.01**	0.38
I	3183±301	71.8±10.0	**0.00000000002**	**≤0.01**	0.023
Rb	18.8±3.3	12.8±0.8	0.09	>0.05	0.68
Sb	0.247±0.085	0.124±0.015	0.166	>0.05	0.5
Sc	0.0059±0.0030	0.0077±0.0020	0.624	>0.05	1.31
Se	3.08±0.33	2.04±0.18	**0.0083**	**≤0.01**	0.66
Zn	111±11	95.1±5.9	0.352	>0.05	0.86

M – arithmetic mean, SEM – standard error of mean, statistically significant values are in bold.

Discussion

As was shown before [27-30,50-52] good agreement of the TEs contents in CRM IAEA H-4 and CRM IAEA HH-1 samples analyzed by instrumental neutron activation analysis with the certified data of these CRMs indicates acceptable accuracy of the results obtained in the study of "normal", "tumor", and "adjacent" groups of thyroid tissue samples presented in Tables 1-4 From Table 2, it was observed that in cancerous tissue the mass fraction of I was 25.6 times lower, whereas mass fractions of Ag, Co, Cr, Hg, and Rb were approximately 13, 1.4, 1.6, 20 and 1.7 times, respectively, higher than in normal tissues of the thyroid. Thus, if we accept the TEs contents in thyroid glands in the "normal" group as a norm, we have to conclude that with a malignant transformation the Ag, Co, Cr, Hg, I, and Rb in thyroid tissue significantly changed. In a general sense Cr, Fe, Sb, Sc, and Zn contents found in the "normal" and "adjacent" groups of thyroid tissue samples were similar (Table 3). However, in the "adjacent" group mean mass fractions of Ag, Co, Hg, I, Rb, and Se were approximately 33, 1.8, 52, 1.7, 2.6, and 1.3 times, respectively, higher, than in the "normal" group. Significant reduced levels of tumor TEs in comparison with thyroid tissue adjacent to tumor were found for Ag, Hg, I, and Se. In malignant tumor Ag, Hg, I, and Se contents were approximately 2.6, 2.6 43, and 1.5 times, respectively, lower than in "adjacent" group of tissue samples (Table 4).

Characteristically, elevated or reduced levels of TEs observed in thyroid nodules are discussed in terms of their potential role in the initiation and promotion of these thyroid lesions. In other words, using the low or high levels of the TEs in affected thyroid tissues researchers try to determine the role of the deficiency or excess of each TE in the etiology and pathogenesis of thyroid diseases. In our opinion, abnormal levels of many TEs in TMNs could be and cause, and also effect of thyroid tissue transformation. From the results of such kind studies, it is not always possible to decide whether the measured decrease or increase in TEs level in pathologically altered tissue is the reason for alterations or vice versa. According to our opinion, investigation of TEs contents in thyroid tissue adjacent to malignant nodules and comparison obtained results with TEs levels typical of "normal" thyroid gland may give additional useful information on the topic because these data show conditions of tissue in which TMNs were originated and developed. Thus, from results obtained, it was possible to conclude that the common characteristics of TMNs in comparison with "normal" thyroid and visually "intact" thyroid tissue adjacent to malignant tumors were drastically reduced level of I (Tables 2-4). It meant that thyroid tissue adjacent to malignant nodules kept the main function of thyroid gland, while malignantly transformed thyroid cells lost its capacity to accumulate I. However, the TEs composition of thyroid tissue adjacent to tumor did not equal TEs contents of "normal" thyroid (Table 3). Moreover, contents of such elements as Ag, Hg, I, and Se in adjacent tissue were higher than in tumor (Table 4). From here, the excessive accumulation of Ag, Hg, I, and Se by thyroid tissue is likely to precede the TMNs origination and development.

Silver

Ag is a TE with no recognized trace metal value in the human body [54]. Food is the major intake source of Ag and this metal is authorized as a food additive (E174) in the EU [55]. Another source of Ag is contact with skin and mucosal surfaces because Ag is widely used in different applications (e.g., jewelry, wound dressings, or eye drops) [56]. Ag in metal form and inorganic Ag compounds ionize in the presence of water, body fluids or tissue exudates. The silver ion Ag+ is biologically active and readily interacts with proteins, amino acid residues, free anions and receptors on mammalian and eukaryotic cell membranes [57]. Besides such the adverse effects of chronic exposure to Ag as a permanent bluish-gray discoloration of the skin (argyria) or eyes (argyrosis), exposure to soluble Ag compounds may produce other toxic effects, including liver and kidney damage, irritation of the eyes, skin, respiratory, and intestinal tract, and changes in blood cells [58]. Experimental studies shown that Ag nanoparticles may affect thyroid hormone metabolism [59]. More detailed knowledge of the Ag toxicity can lead to a better understanding of the impact on human health, including thyroid function.

Cobalt

Health effects of high Co occupational, environmental, dietary and medical exposure are characterized by a complex clinical syndrome, mainly including neurological, cardiovascular and endocrine deficits, including hypothyroidism [60,61]. Co is genotoxic and carcinogenic, mainly caused by oxidative DNA damage by reactive oxygen species, perhaps combined with inhibition of DNA repair [62]. In our previous studies it was found a significant age-related increase of Co content in female thyroid [29]. Therefore, a goitrogenic and, probably, carcinogenic effect of excessive Co level in the thyroid of old females was assumed. Elevated level of Coin TMNs, observed in the present study, supports this conclusion. Anyway, the accumulation of Coin malignant thyroid tumors could possibly be explored for diagnosis of TMNs.

Chromium

The general population can be exposed to low levels of Cr primarily through consumption of food and to a lesser degree through inhalation of ambient air and ingestion of drinking water [63]. Cr-compounds are cytotoxic, genotoxic, and carcinogenic in nature. Some Cr forms, including hexavalent chromium (Cr6+), are toxicants known for their carcinogenic effect in humans. They have been classified as certain or probable carcinogens by the International Agency for Research on Cancer [64]. The lung cancer risk is prevalent in pigment chromate handlers, ferrochromium production workers, stainless steel welders, and chrome-platers [65]. Except in Cr-related industries and associated environments, Cr intoxication from environmental exposure is not common. However, it was found, that drinking water supplies in many geographic areas contain chromium in the +3 and +6 oxidation states. Exposure of animals to Cr6+ in drinking water induced tumors in the mouse small intestine [66]. Many other animal experiments and in vitro studies demonstrate also that Cr can induce oxidative stress and exert cytotoxic effects [67]. Besides reactive oxygen species (ROS) generation, oxidative stress, and cytotoxic effects of Cr exposure, a variety of other changes like DNA damage, increased formation of DNA adducts and DNA-protein cross-links, DNA strand breaks, chromosomal aberrations and instability, disruption of mitotic cell division, chromosomal aberration, premature cell division, S or G2/M cell cycle phase arrest, and carcinogenesis also occur in humans or experimental test systems [65]. Anyway, the accumulation of Cr in malignant thyroid tumors could possibly be explored for diagnosis of TMNs.

Mercury

In the general population, potential sources of Hg exposure include the inhalation of this metal vapor in the air, ingestion of contaminated foods and drinking water, and exposure to dental amalgam through dental care [68]. Hg is one of the most dangerous environmental pollutants [69]. The growing use of this metal in diverse areas of industry has resulted in a significant increase of environment contamination and episodes of human intoxication. Many experimental and occupational studies of Hg in different chemical states shown significant alterations in thyroid hormones metabolism and thyroid gland parenchyma [70,71]. Moreover, Hg was classified as certain or probable carcinogen by the International Agency for Research on Cancer [72]. For example, in Hg polluted area thyroid cancer incidence was almost 2 times higher than in adjacent control areas [73].

Iodine

To date, it was well established that iodine deficiency or excess has severe consequences on human health and associated with the presence of TMNs [4-8,74-76]. In present study elevated level of I in thyroid tissue adjacent to malignant tumor and drastically reduced I mass fraction in cancerous tissue was found in comparison with "normal" thyroid. Compared to other soft tissues, the human thyroid gland has higher levels of I, because this element plays an important role in its normal functions, through the production of thyroid hormones (thyroxin and triiodothyronine) which are essential for cellular oxidation, growth, reproduction, and the activity of the central and autonomic nervous system. As was shown in present study, malignant transformation is accompanied by a significant loss of tissue-specific functional features, which leads to a drastically reduction in I content associated with functional characteristics of the human thyroid tissue. On the one hand, significantly high level of I in thyroid tissue adjacent to malignant tumor may indicate an involvement of I excess in carcinogenesis. But, on the other hand, because the malignant part of gland stopped to produce thyroid hormones, the rest "intact" part of thyroid tries to compensate thyroid hormones deficiency and work more intensive than usual. The intensive work may explain elevated level of I in thyroid tissue adjacent to malignant tumor in comparison with thyroid tissue of "normal" gland. Drastically reduced level of I content in cancerous tissue could possibly be explored for differential diagnosis of benign and malignant thyroid nodules, because, as was found in our earlier studies, thyroid benign transformation (goiter, thyroiditis, and adenoma) is accompanied by a little loss of I accumulation [42-46].

Rubidium

There is very little information about Rb effects on thyroid function. Rb as a monovalent cation Rb+ is transferred through membrane by the Na+K+-ATPase pump like K+ and concentrated in the intracellular space of cells. Thus, Rb seems to be more intensively concentrated in the intracellular space of cells. The source of Rb elevated level in tumor and adjacent to tumor tissue may be Rb environment overload. The excessive Rb intake may result a replacement of medium potassium by Rb, which effects on iodide transport and iodoaminoacid synthesis by thyroid [77]. The source of Rb increase in TMNs tissue may be not only the excessive intake of this TE in organism from the environment, but also changed Na+K+ -ATPase or H+K+ - ATPase pump membrane transport systems for monovalent cations, which can be stimulated by endocrine system, including thyroid hormones [78]. It was found also that Rb has some function in immune responce [79] and that elevated concentration of Rb could modulate proliferative responses of the cell, as was shown for bone marrow leukocytes [80]. These data partially clarify the possible role of Rb in etiology and pathogenesis of TMNs.

Selinium

The high level of Se content found just in thyroid tissue adjacent to malignant tumor cannot be regarded as pure chance. The selenoprotein characterized as Se-dependent glutathione peroxidase (Se-GSH-Px) is involved in protecting cells from peroxidative damage. This enzyme may reduce tissue concentration of free radicals and hydroperoxides. It is particular important for the thyroid gland, because thyroidal functions involve oxidation of iodide, which is incorporated into thyroglobulin, the precursor of the thyroid hormones. For oxidation of iodide thyroidal cells produce a specific thyroid peroxidase using of physiologically generated hydrogen-peroxide (H2O2) as a cofactor [81]. It follows that the thyroid parenchyma must be continuously exposed to a physiological generation of H2O2 and in normal conditions must be a balance between levels of Se (as Se-GSH-Px) and H2O2. The elevated level of Se in thyroid tissue adjacent to malignant nodules was accompanied excessive accumulation of Ag, Co, Hg, I, and Rb in comparison with "normal" values for these elements. Moreover, contents of Ag, Co, Hg, I, and Rb in adjacent tissue were higher than in malignant nodules. Thus, it might be assumed that the elevated level of Se is reaction of adjacent tissue on an increase in concentration of free radicals and hydroperoxides in thyroid gland and that this increase preceded the TMNs origination and development.

Limitations

This study has several limitations. Firstly, analytical techniques employed in this study measure only eleven TEs (Ag, Co, Cr, Fe, Hg, I, Rb, Sb, Sc, Se, and Zn) mass fractions. Future studies should be directed toward using other analytical methods which will extend the list of TEs investigated in "normal" thyroid and in pathologically altered tissue. Secondly, the sample size of TMNs group was relatively small and prevented investigations of TEs contents in this group using differentials like gender, histological types of TMNs, tumor functional activity, stage of disease, and dietary habits of patients with TMNs. Lastly, generalization of our results may be limited to Russian population. Despite these limitations, this study provides evidence on many TEs level alteration in malignant tumor and adjacent to tumor tissue and shows the necessity to continue TEs research of TMNs.

Conclusion

In this work, TEs analysis was carried out in the tissue samples of TMNs using neutron activation analysis. It was shown that neutron activation analysis is an adequate analytical tool for the non-destructive determination of Ag, Co, Cr, Fe, Hg, I, Rb, Sb, Sc, Se, and Zn content in the tissue samples of human thyroid in norm and pathology, including needle-biopsy specimens. It was observed that in malignant tissue the mass fraction of I was 25.6 times lower, whereas mass fractions of Ag, Co, Cr, Hg, and Rb were approximately 13, 1.4, 1.6, 20 and 1.7 times, respectively, higher than in normal tissues of the thyroid. In a general sense Cr, Fe, Sb, Sc, and Zn contents found in the "normal" and "adjacent" groups of thyroid tissue samples were similar. However, in the "adjacent" group mean mass fractions of Ag, Co, Hg, I, Rb, and Se were approximately 33, 1.8, 52, 1.7, 2.6, and 1.3 times, respectively, higher, than in the "normal" group. Significant reduced levels of tumor TEs in comparison with thyroid tissue adjacent to tumor were found for Ag, Hg, I, and Se. In malignant tumor Ag, Hg, I, and Se contents were approximately 2.6, 2.6, 43, 1.5, and 1.5 times, respectively, lower than in "adjacent" group of tissue samples. It was supposed that the drastically reduced level of I, as well as elevated levels of Ag, Co, Cr, Hg, and Rb in cancerous tissue could possibly be explored for differential diagnosis of benign and malignant thyroid nodules.

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Conflict of Interest

The author has not declared any conflict of interests.

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