An Innovative Multidisciplinary Approach to Thyroid Research: Modern Problems and Solutions

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Abstract. A 15-year, innovative, multidisciplinary experimental and theoretical study was conducted to investigate the peculiarities of thyroid functioning at the systemic-somatic, tissue-organ, and organelle-cell levels of the structural and functional hierarchy, focusing on the correction of hypo- and hyperthyroidism with organic and inorganic iodine. The object of the study was the thyroid glands, liver, adrenal glands, and body weight of male albino rats. Basic biomedical, histological, histochemical, and electron microscopic methods were used. On the systemic-somatic level, Spearman's correlation analysis revealed that the thyroid gland, adrenal glands, and liver constitute an integral "functional module"; regression analysis proved that changes in the weight of these organs have a provable impact on changes in body weight. Research at the tissue-organ level has improved and expanded the existing data on biochemical and histochemical features of thyroid hormone production. The presented work highlights the results of the research on follicular cells on the organelle-cell level. The use of the principles of cluster analysis and fuzzy logic, the principle of phase interval, mathematical statistics, and Pearson's correlation analysis as a package of specially selected mathematical methods formed the basis of the author's methods – semi-quantitative analysis of electronograms and determination of hormonopoietic cells' special capabilities profiles. The correlation portraits of connections between organelles, implementing the synthetic, secretory, transport, and energy activities of follicular cells, were created with their help. These portraits served to research the peculiarities of cell components' interactions, making it possible to expand the fundamental understanding of the mechanisms regulating thyroid hormone production. The features of the thyroid gland functioning while taking organic and inorganic iodine formed the basis of recommendations for the prevention and correction of iodine deficiency states with iodine of different chemical natures.

Keywords: thyroid gland, follicular cell, cell organelles, hypothyroidism, hyperthyroidism, organic iodine, inorganic iodine, correlation portrait.

Introduction. The current stage of biomedicine's development is characterized by the expansion of the range of research methods; at the same time, mathematical methods are becoming increasingly important [1,2]. According to the general theory of systems, the body, as a complex biological self-regulating supersystem, is an integrative set of combined systems. We consider these systems on three levels of the structural and functional hierarchy, which, from the standpoint of cybernetic concepts, makes it possible to research the peculiarities of each level. Thus, the thyroid gland as a complex self-regulating system simultaneously functions on the three levels of the hierarchy, which we defined as organelle-cell, tissue-organ, and systemic-somatic [3]. In the study of the thyroid gland on the organelle-cell level, we researched the morphofunctional features of follicular cells; on the tissue-organ level – the activity of the thyroid gland as a hormone-producing organ; on the systemic-somatic level – the activity of the complex "thyroid gland – functionally related organs – organism" (Table 1). This scientific area requires multidisciplinary research in various fields of medicine [4,5].

Thyroid hormones are critically important for most vital processes due to their importance in maintaining homeostasis and adaptation of the body. Through the hypothalamic-pituitary axis, the thyroid gland is functionally connected to other endocrine organs and the brain. At the same time, recent data show a steady upward trend in thyroid pathology worldwide. It is caused by a variety of factors, including the high sensitivity of the thyroid gland to anthropogenic and technogenic influences, which gives grounds to consider its morphofunctional state as an indicator of environmental pollution and environmental stress [6]. However, the main factor that regulates thyroid activity is iodine intake. Thyroid diseases affect an estimated 200 million people worldwide. It is considered that due to the biogeochemical characteristics of soils, 40% of the world's population, i.e., more than 2.8 billion people, are at risk of pathological conditions caused by iodine deficiency [7], which makes it an important cause of physical, somatic, and cognitive-intellectual pathology. A recognized measure for the prevention of iodine deficiency is the iodization of food products, which is traditionally carried out with inorganic iodine compounds. In Europe, potassium iodate is mainly used, while in Asia, potassium iodide is used. Currently, the possibility of using organic iodine is being considered, and seaweed is considered a particularly promising source. Regarding the above-mentioned, the need to research the peculiarities of iodine of different chemical natures on the thyroid gland is very relevant. The studies of the tissue-organ level can be found in [8,9], and the systemic-somatic level in [10-16].

Table 1. Structural hierarchy of the "thyroid gland system" and methods of its study.

No.	Biological system/ level	Representative of the hierarchy	Method of research	Object of research
I	Cellular/ organelle-cell	Follicular cell	Electron microscopy of thyroid gland [17-19]	Electron microscope images
		Cell components	• Semi-quantitative analysis of electronograms according to Rabuka [20] • Rabuka's method for determining the profiles of hormonopoietic cells' special capabilities [20]	• Synthetic capability profile of follicular cells • Secretory capability profile of follicular cells • Transport capability profile of follicular cells • Energy capability profile of follicular cells
II	Organ/ tissue-organ	Thyroid gland	Histochemical method [21]	Activity of intrafollicular colloid
III	Whole-organism/ systemic-somatic	Thyroid gland	Weighing	Organ weight, Organ coefficient
			Volumetric analysis [22]	Volumetric determination of Inorganic iodine
		Adrenal glands	Weighing	Organ weight, Organ coefficient
			Volumetric analysis [23]	Volumetric determination of Ascorbic acid
		Liver	Weighing	Organ weight, Organ coefficient
			Volumetric analysis [23]	Volumetric determination of Ascorbic acid
		Body	Weighing	Changes in body weight

This article highlights the achievements of the research on the organelle-cell level of the thyroid gland.

The purpose of the study was to examine the mechanisms of impact of organic and inorganic iodine on various aspects of the follicular cell activity as a structural subsystem of the thyroid gland, the *task of research* – to determine the peculiarities of the relationships between the components of the formalized directions of follicular cell activity while consuming different amounts of organic and inorganic iodine under certain model conditions, and to adapt the established interactions to the position of cytophysiology.

Materials and methods. We conducted a comprehensive study of various aspects of follicular cell activity when taking organic and inorganic iodine under different model conditions using a package of mathematical methods developed by us, which is a qualitatively higher stage of cognition of the consistent patterns and features of the functioning of biological objects. The research tool used was an expert approach developed by us, in which the study of follicular cell activity is carried out in successive steps, which become the basis for creating hypotheses that can explain the main patterns of its activity. Since each element of the body has inherent morphofunctional characteristics, the properties of these characteristics and the dependencies between them can be described using certain parameters and variables. At the same time, normal and pathological processes have a series of interrelated features that determine the way the biological "follicular cell system" functions, which is most appropriate in terms of its structure and potential.

Following the aim and task of research, the effect of organic and inorganic iodine was studied in three series of 30-day experiments in the spring-summer. Nonlinear male albino rats with an initial weight of 140-160 g consumed a basal semi-synthetic starch and casein diet. Essential macro- and microelements were supplied in the diet with the classic salt mixture 12 by J.H. Jones & C. Foster [24], from which potassium iodide was removed to create iodine deficiency. The state of iodine deficiency was created by removing iodine from the salt mixture (1st series of studies), the state of potential iodine deficiency was created by adding *Thiamazole* to the iodine-deficient diet at an approved dose of 3 mg/kg body weight (2nd series of studies), and hyperthyroidism was created by adding *Desiccated Thyroid Extract* to the iodine-deficient diet at an approved dose of 15 mg/100 g body weight (3rd series of studies). The rats consumed histologically determined doses of organic and inorganic iodine: low (21 μg/kg body weight) – we call it "minimally effective dose" [25,26], moderate (50 μg/kg body weight), and high (100 μg/kg body weight). The rats of the control groups (K1, K2, K3) were not given additional iodine in their food. The source of organic iodine in the diet was an *iodine-protein components* (iodine-protein food supplement) from the red Black Sea algae *Phyllophora nervosa* [27,28]. Inorganic iodine was supplied by potassium iodide.

The features of the thyroid tissue were studied by electron microscopy. The information obtained was used to further create correlation portraits of the profiles of different directions of follicular cell activity. The results obtained in each series of studies were compared: (1) with similar data from intact rats; (2) with data from rats in control groups; (3) with data from rats receiving other doses of the studied iodine-containing agent; (4) with data from rats receiving similar doses of iodine with another iodine-containing agent. The data obtained were subjected to mathematical processing with subsequent analysis and interpretation. The criterion for evaluating the results was their approximation to similar indicators of intact rats while moving away from the indicators in the corresponding control group.

Table 2. The synthetic capability profile of the follicular cell.

Cluster	Data	Status	Symbol
Cytoplasm	electron density	decreased	B1
		moderate	B2
		increased	B3
Rough endoplasmic reticulum (rough ER)	width of components	constricted	J1
		moderate	J2
		expanded	J3
	number of fixed ribosomes	decreased	J4
		moderate	J5
		increased	J6

Free ribosomes and polysomes	number	decreased	K1
		moderate	K2
		increased	K3
Golgi body	width of components	constricted	L1
		moderate	L2
		expanded	L3

The examination results of electronograms are traditionally presented in linguistic (qualitative) form. However, both the stating and summarizing parts of such an examination largely depend on the experience, qualifications, and priorities of the researcher, which can lead to subjectivity in the interpretation of the results. The principles of fuzzy logic cannot always be fully applied when dealing with biological systems, as they imply the existence of strict determinism, which is difficult to achieve when the body needs to constantly maintain dynamic equilibrium. Given this, the implementation of our method of semi-quantitative analysis of electronograms allows transforming the linguistic description of the electron microscopy image (qualitative and binary data) into digital equivalents (quantitative indicators), which objectifies the result obtained, significantly expands the information about the object under study and is the basis of another author's method – determination of hormonopoietic cells' special capabilities profiles.

The mathematical approach we have developed to study the activity of the thyroid gland at the organelle-cell level of hierarchical organization involves the consistent application of certain mathematical methods. The study was carried out in five steps. Step 1: According to the basics of cytophysiology, clusters are distinguished from the entire set of follicular cell components, which are groups of organelles that implement specific directions of activity; this is how clusters of their synthetic, secretory, transport, and energy capabilities are formed. Capability profiles are ranked components of capability clusters of the corresponding direction (Tables 2, 3, 4, 5).

Table 3. The secretory capability profile of the follicular cell.

Cluster	Data	Status	Symbol
Intrafollicular colloid	electron density	decreased	E1
		moderate	E2
		increased	E3
Apical microvilli	number	decreased	H1
		moderate	H2
		increased	H3
	compactness of location, length	decreased	H4
		moderate	H5
		increased	H6
Lysosomes	number	decreased	G1
		moderate	G2
		increased	G3
	size	small	G4
		medium	G5
		large	G6
	electron density	decreased	G7
		moderate	G8
		increased	G9
Secretory vesicles	number	decreased	M1
		moderate	M2
		increased	M3
	electron density	decreased	M4
		moderate	M5

		increased	M6
	localization	apical pole	M7
		all over the cytoplasm	M8
	topographic connectivity with lysosomes	absent	M9
		present	M10

Step 2: At the principle of phase interval, after visualization of all elements of the studied cluster, their qualitative comparative quantification is performed in terms of proximity to two standards (“norm” and “pathology”), which are electronograms of follicular cells of intact rats and rats with uncorrected pathology. Step 3: Transforming qualitative indicators (linguistic) into quantitative (digital) ones – in each cluster, according to the principle of fuzzy logic, ranking the degrees of manifestation of the properties of each element, carrying out their digital evaluation according to the point scale developed by us, and averaging them using mathematical statistics; according to the results obtained, the absence of a feature is 0 points, a weak manifestation is 1 point, a moderate manifestation is 2 points, a significant manifestation is 3 points, and the maximum is 4 points. At the same time, when synthetic processes are stimulated, the number of ribosomes (fixed and free) can significantly increase. In this case, with the maximum degree of activation of hormonopoiesis by organic or inorganic iodine, an increase in the index to 8 points (200%) is possible.

Table 4. The transport capability profile of the follicular cell.

Cluster	Data	Status	Symbol
Basal cell membrane	tortuosity	insignificant	P1
		moderate	P2
		significant	P3
Pericapillary space [29]	width	decreased	Q1
		moderate	Q2
		increased	Q3
	inclusions	present	Q4
		absent	Q5
Endotheliocytes	morpho-functional state	hypotrophic	R1
		normal	R2
		hypertrophic	R3
	size of pseudopods	small	R4
		medium	R5
		large	R6
Perifollicular capillaries	capillary lumen	moderate electron density	S1
		increased electron density	S2
		single erythrocytes (0-2)	S3
		erythrocytes (2-4) in a group without adhesion	S4
		presence of basophiles	S5
		presence of single fibrin strands	S6

Step 4: Within each cluster, a Pearson’s correlation analysis is performed, which searches for connections between cluster elements, determines their positive or negative direction, using the Chaddock scale [30] of linear correlation to determine the closeness (strength) of the traced associations. The most significant are very high and high associations, which on the scale are within the range of $0.91 \le r \le 1.0$ and $0.71 \le r \le 0.9$, respectively; in the absence of such correlations,

marked associations ($0.51 \le r \le 0.7$) and moderate associations ($0.31 \le r \le 0.5$) are taken into consideration. Based on the data obtained, correlation portraits of the studied profile are created in a tabular or graphical form [31].

Step 5: Analysis of the created correlation portraits, during which the data on the functional state of each element of the profile of the studied capability and the connections between them are interpreted, the approximation of the portrait to the characteristics of normality or pathology is assessed, and the interdependencies between the components of the portrait and the architectonics of the portrait as a whole are generalized, the mechanisms of activity of the elements of the studied cluster are determined. In interpreting the relationships in the correlation portraits, we used cytophysiology data, as well as basic concepts of biological systems and approaches to their study in normal and pathological conditions, according to which any system is characterized by the properties of its elements, the degree of their manifestation, and the direction and strength of connections between the elements of the system.

Table 5. The energy capability profile of the follicular cell.

Cluster	Data	Status	Symbol
Mitochondria	number	decreased	N1
		moderate	N2
		increased	N3
	shape	round	N4
		oval	N5
		finger-like	N6
		Y-like	N7
	size	small	N8
		medium	N9
		large	N10
	topographic connectivity with rough ER and the Golgi body	absent	N11
		present	N12
	degenerative changes	absent	N13
		present	N14
Mitochondrial cristae	contour	indistinct	N15
		distinct	N16
	number of mitoribosomes	absent	N17
		decreased	N18
		moderate	N19
		increased	N20
Mitochondrial matrix	structure	homogeneous	N21
		granular	N22
	electron density	decreased	N23
		moderate	N24
		increased	N25

Results and discussion. To present the research, a monograph chapter is required. Therefore, the number of correlation portraits is minimal, and the results and their discussion are presented unconventionally without mathematical data. Detailed information is available in our other articles.

• ***The synthetic direction of follicular cells' activity.*** Under the conditions of organic iodine intake against the background of iodine deficiency and potentiated iodine deficiency caused by the *Thiamazole* thyrostatic drug, the main indicators of the synthetic activity of follicular cells were the number of free ribosomes and polysomes in the cytoplasm, fixed ribosomes on the membranes of rough endoplasmic reticulum (rough ER), and the coherence of functional states of rough ER and

Golgi body; we consider the same functional state of their structures to be a manifestation of the latter. Discrepancy in the degree of manifestation of functional states of the structures of the main hormone-synthesizing organelles, the number of free and fixed ribosomes with the functional states of the structures of rough ER and Golgi body, and the discrepancy between the states and quantities of these cellular components and the degree of electron density of the cytoplasm are considered to be signs of a violation of the synthetic activity of the follicular cell – its insufficient possibility or cellular stress arising during functioning. The intake of an iodine-enriched diet showed that the functional state of follicular cell components that promoted or impeded its synthetic activity was determined by the chemical nature and dose of iodine consumed (Figs. 1a, 2a, 3a): organic iodine activated hormonopoietic ultrastructures more than inorganic iodine [25,32,33].

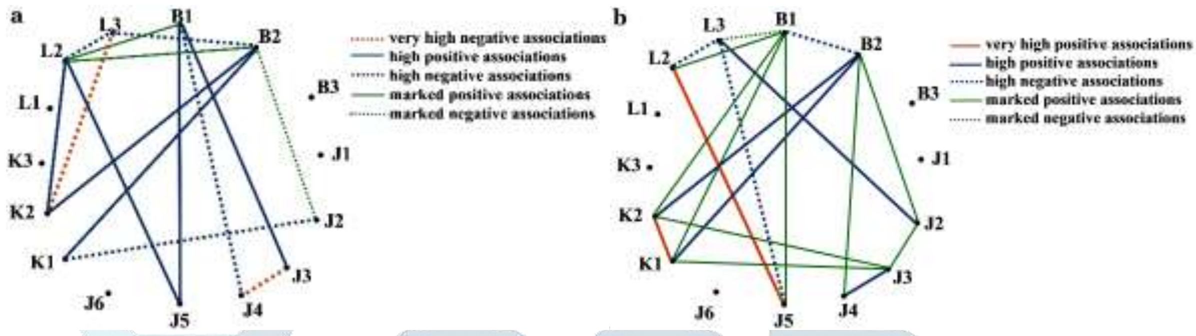


Fig. 1. Correlation portrait of the follicular cell synthetic capability profile under the consumption of a low dose of organic (**a**) and inorganic (**b**) iodine in conditions of iodine deficiency.

The architectonics of graphical correlation portraits of the synthetic capability profile when taking organic iodine, testified to both the sufficient stability of the system and its possibility for alteration. We attribute this feature of the architectonics ("plasticity") to the activation of the hormone synthesis area of the cell's activity, which is a manifestation of adaptive mechanisms that contribute to the realization of its synthetic possibility.

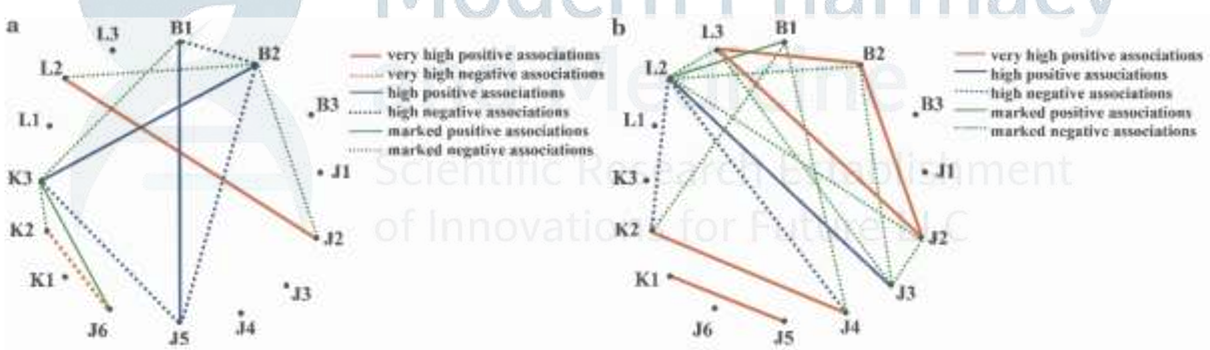


Fig. 2. Correlation portrait of the follicular cell synthetic capability profile under the consumption of a moderate dose of organic (**a**) and inorganic (**b**) iodine in conditions of iodine deficiency.

When inorganic iodine was administered, the structure of the correlation portraits of the profile of synthetic capability follicular cells indicated the presence of a certain reserve of lability (as indicated by negative associations), but they were characterized by greater rigidity than the portraits created when similar doses of organic iodine were consumed. This feature of the structure of correlation portraits indicates that in hypothyroidism, inorganic iodine intake does not involve all available intrathyroid mechanisms in the process of thyroid hormone synthesis (Figs. 1b, 2b, 3b).

Under the conditions of potentiated iodine deficiency, the synthetic activity of follicular cells depended to a greater extent on the dose of iodine consumed and to a lesser extent on its chemical nature. The addition of moderate and high doses of organic or inorganic iodine to the diet led to the appearance of correlations that indicated inconsistencies in the functional states of the main protein-synthesizing structures of the follicular cell – rough ER and Golgi body. When inorganic iodine was administered, these were links that the decreased electron density of the cytoplasm formed simultaneously with both moderate width and expanded structures of rough ER; a moderate number of fixed ribosomes – with expanded structures of the rough ER, with moderate width and expanded components of Golgi body; moderately expanded structures of rough ER – with a small number of fixed ribosomes.

When similar doses of organic iodine were consumed, the main relationships that indicated this discrepancy were the connections of moderate width of rough ER structures with narrowed components of the Golgi body and decreased number of free ribosomes, and the connections of decreased cytoplasmic electron density with moderate and decreased number of free ribosomes.

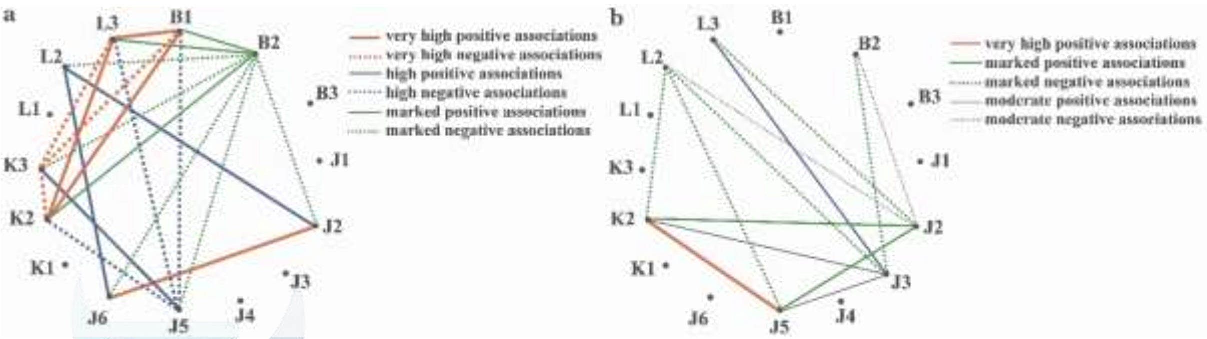


Fig. 3. Correlation portrait of the follicular cell synthetic capability profile under the consumption of a high dose of organic (**a**) and inorganic (**b**) iodine in conditions of iodine deficiency.

Intake of moderate and high doses of organic and inorganic iodine against the background of increased functional activity of the thyroid gland was expected to cause functional cellular stress of the follicular cell, as evidenced by the connections of expanded components of the Golgi body with expanded rough ER structures and a moderate number of free and fixed ribosomes. The fact that hormone synthesis is a fundamental activity of the follicular cell, even under adverse conditions, is confirmed by a significant number of correlations between the elements of the profile of the discussed capability. We believe that it is logical to interpret this not only as a sign of functional activity or stress, but also as a manifestation of adaptive mechanisms designed to maintain synthetic activity under conditions that disrupt it. An example of such mechanisms for ensuring the activity of the follicular cell under increased functional cellular stress is the correlation between protein-synthesizing structures with different degrees of functional activity.

A low dose of organic iodine contributed to the formation of correlations between moderately expanded rough ER structures and a moderate number of free ribosomes, moderately expanded Golgi body components, and a moderate number of fixed ribosomes, which, under the conditions of hyperthyroidism discussed, may indicate an optimization of protein synthesis. This can be confirmed by the architectonics of correlation portraits of the studied capability, which was simultaneously characterized by both stability and moderate lability (Fig. 4a).

With the consumption of a similar dose of inorganic iodine, correlations were observed indicating the preservation of impaired synthetic activity, which, in our opinion, was manifested by a noticeable rigidity of the architectonics of the structure of correlation portraits (Fig. 4b). It is important to note that in hyperthyroidism, the use of inorganic iodine contributed more to the formation of such adaptive relationships than the use of organic iodine.

We believe it is necessary to emphasise the importance that certain groups of correlations can acquire. These are the relationships traced between the localization and number of fixed and free ribosomes and other constituent elements of the profile, as well as the connections of different degrees of cytoplasmic electron density with the characteristics of the states of protein-synthesizing structures, and the connections of Golgi body components with structures of rough ER in their different functional states [34].

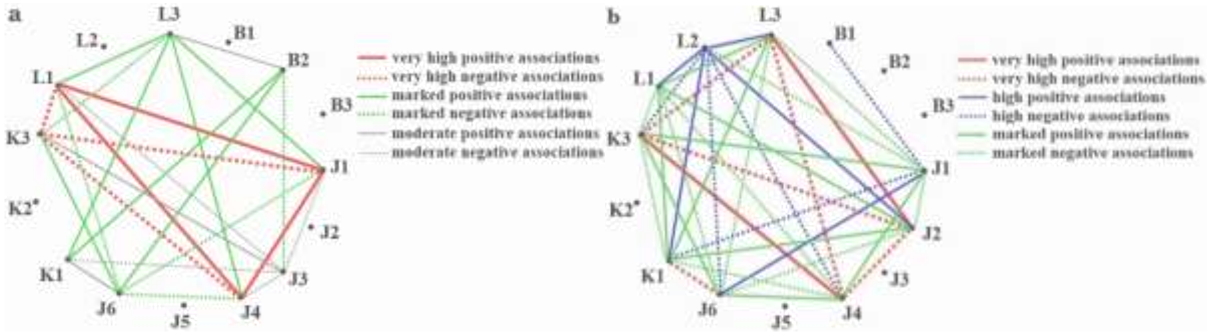


Fig. 4. Correlation portrait of the profile of the synthetic capability of follicular cells under the consumption of a low dose of organic (**a**) and inorganic (**b**) iodine in conditions of functional hyperthyroidism.

• ***The secretory direction of follicular cells' activity.*** The use of iodine promoted the secretion of the produced hormonal product, while the signs of cellular stress in secretory activity depended on the conditions of the study and changed accordingly (Figs. 5a, 5b) [35]. When taking organic iodine, the improvement of secretion was indicated by a significant number of functionally relevant correlations traced between the elements of the profile. Under conditions of iodine deficiency and potentiated iodine deficiency, they consisted of the peculiarities of lysosomal connections with secretory vesicles and apical membrane microvilli, as well as connections of apical microvilli with intrafollicular colloid and secretory vesicles.

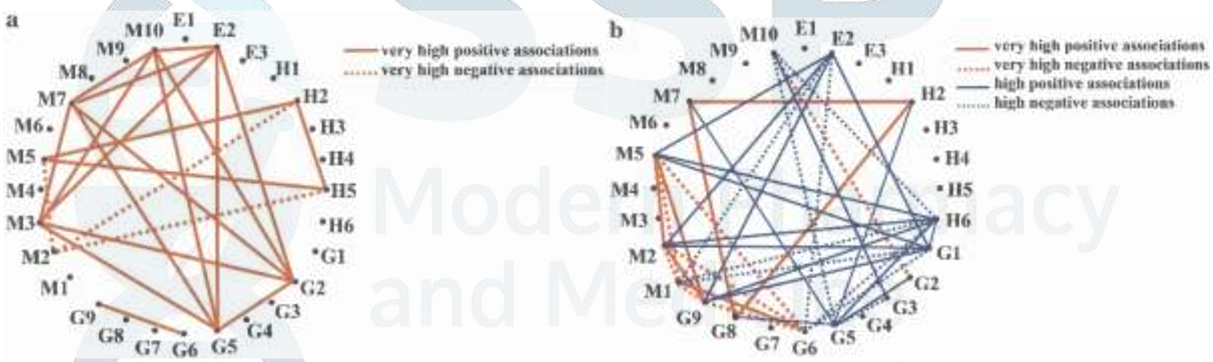


Fig. 5. Correlation portrait of the follicular cell secretory capability profile under the consumption of a moderate dose of organic (**a**) and inorganic (**b**) iodine in conditions of iodine deficiency.

Under conditions of hyperthyroidism with a low and moderate doses of iodine, the presence of stress in hormone secretion was indicated by complexes of negative associations that microvilli had with increased and moderate electron density of the intrafollicular colloid, apical localization of secretory vesicles and their moderate electron density; at high iodine intake – the connections that the decreased and moderate electron density of lysosomes had with the apical localization of secretory vesicles, and with their distribution all over the cytoplasm.

While taking inorganic iodine, there was some inconsistency in the activity of secretory structures, as indicated by correlations with insufficient functional expediency. We consider the connections of apical microvilli with secretory vesicles evenly distributed throughout all over the cytoplasm, a mismatch of functional states of apical microvilli and secretory vesicles, connections between lysosomes and secretory vesicles of different numbers, sizes, and electron density, and disruption of topographic connectivity between secretory vesicles and lysosomes to be the connections indicating functional stress during hormone secretion. Another feature of the correlation portraits of the secretory capability profiles of follicular cells under inorganic iodine administration was the large number of very high associations (Fig. 5b). Structures formed by this type are prone to inlability, which can make it difficult, restrictive, or even impossible for them to adapt to changing conditions, for example, in a pathological process.

The list of profile elements that were in a certain relationship with each other, in particular, the presence of connections, their strength, and direction, was also determined by the study conditions. Under conditions of iodine deficiency, when taking a low dose of organic iodine, apical microvilli had the most connections, when taking a moderate dose of iodine – the electron density of colloid, secretory vesicles, and lysosomes, and when taking a high dose – lysosomes. Under conditions of potentiated iodine deficiency, the dependence of the composition of portraits on the dose of iodine intake was levelled; apical microvilli had the highest number of connections. Under conditions of hyperthyroidism, the composition of correlation portraits did not depend on the dose of organic iodine consumed: all elements of the secretory capability profile were involved in their formation.

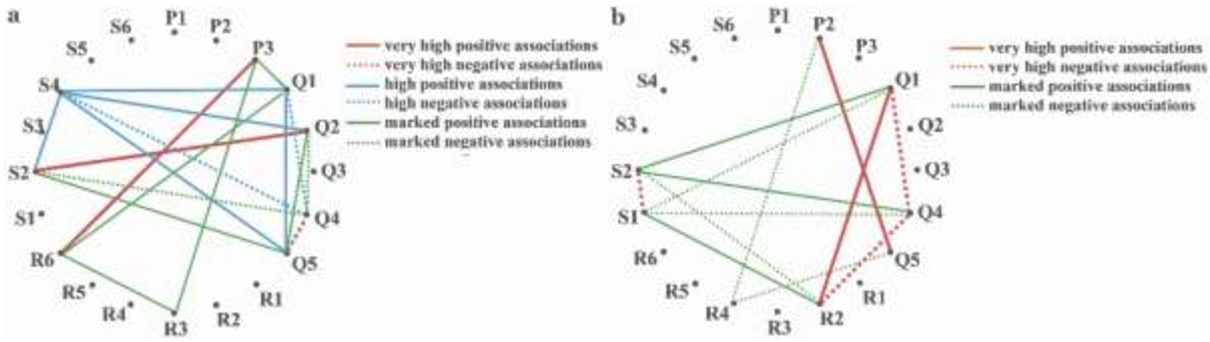
The effect of inorganic iodine on the composition of the correlation profile portraits was different. Under conditions of iodine deficiency, regardless of the dose of iodine consumed, the most functional significance was given to the connections of apical microvilli; under conditions of potentiated iodine deficiency – to the connections of colloid electron density (at low and high doses) and apical microvilli; under conditions of hyperthyroidism c to the connections of lysosomes and secretory vesicles. We can offer several explanations for those structural features of the profile. Firstly, iodine of different chemical natures can selectively affect different cellular structures of the same functional orientation. Secondly, different amounts of iodine consumed can have different strengths of effect, and thirdly, the possibility of implementing a certain orientation is determined by the conditions in which the system under study is located.

Thus, the morphological state of the follicular cell structures that secrete the hormone was highly dependent on the conditions in which the body was in – iodine deficiency, potentiated iodine deficiency, or hyperthyroidism. At the same time, the specifics of their response to iodine intake depended on the ability of iodine of a certain chemical nature to selectively affect certain structures of follicular cells. In general, organic iodine had the ability to increase the secretion of thyroid hormones, and inorganic iodine – to slow down a bit.

• ***The transport direction of follicular cells' activity.*** Iodine consumption activated intracellular adaptive mechanisms aimed at improving the transport of produced hormones and creating conditions that could optimize the bloodstream in perifollicular capillaries (Figs. 6a, 6b, 6c) [36]. These mechanisms themselves were highly dependent on the functional state of the thyroid gland. In conditions of iodine deficiency and potentiated iodine deficiency, they did not depend on the chemical nature of the consumed iodine and consisted of an increase in the tortuosity of the basal membranes of follicular cells and the width of pericapillary space, large sizes of endothelial pseudopodia, and an increase in the number of red blood cells in the capillary lumen.

The peculiarities of these adaptive mechanisms were largely determined by the chemical nature of the iodine consumed (Figs. 7a, 7b) [37]. Thus, the consumption of organic iodine contributed to the optimization of connections between follicular cells and perifollicular capillaries.

Considering the current information on the ability of erythrocyte membranes to fix and transport thyroid hormones, the increase in connections of erythrocytes and basophils with other elements of the profile observed with the consumption of inorganic iodine, we believe that inorganic iodine is an important mechanism for improving microcirculation and an effective adaptation in providing the body with thyroid hormones. Under conditions of hyperthyroidism, the transport possibility of follicular cells was the highest while taking a low dose of organic and inorganic iodine.



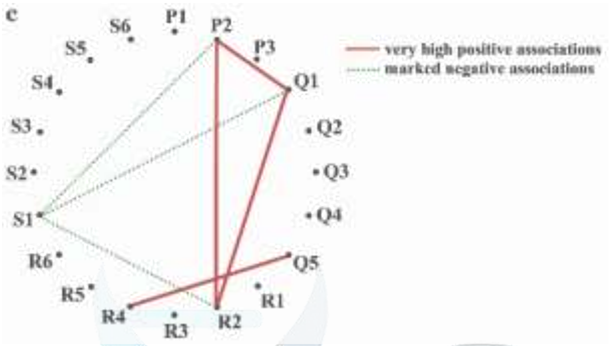


Fig. 6. Correlation portrait of the follicular cell transport capability profile under the consumption of a low dose (**a**), moderate dose (**b**), and high dose (**c**) of organic iodine in conditions of *Thiamazole*-potentiated iodine deficiency.

The peculiarities of the effect of organic iodine were a greater number of correlations that formed the tortuosity of the basal membrane of follicular cells, the width and state of the pericapillary space, and the growth of their interdependence. Inorganic iodine intake increased the number of connections in basophils and erythrocytes; a tendency to stasis and microclusters of erythrocytes was observed in perifollicular capillaries.

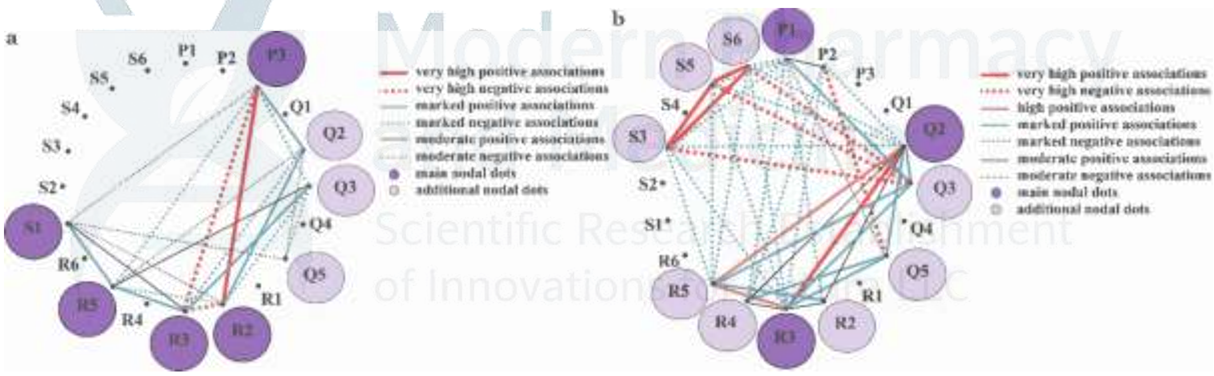


Fig. 7. Correlation portrait of the follicular cell transport capability profile under the consumption of a low dose of organic (**a**) and inorganic (**b**) iodine in conditions of iodine deficiency (representation of the nodal dots).

• ***The energy direction of follicular cells' activity.*** Consumption of organic and inorganic iodine increased the imbalanced energy possibility of follicular cells. Under conditions of iodine deficiency and potentiated iodine deficiency, the main signs of increased energy maintenance of intracellular processes were an increase in the number of mitochondria and ribosomes on their crystae, a decrease in degenerative changes in mitochondria, restoration of the granular structure of mitochondrial matrix and the topographic connectivity of mitochondria with the rough ER and Golgi body (Fig. 8a). The energy possibility of follicular cells under inorganic iodine administration was somewhat lower than under similar doses of organic iodine. This was indicated by the smaller number of mitochondria and ribosomes on their cristae, preservation of altered mitochondria in some follicular cells, and a disturbed topographic connectivity between the main structures of the energy maintenance of the cell (Fig. 8b) [38].

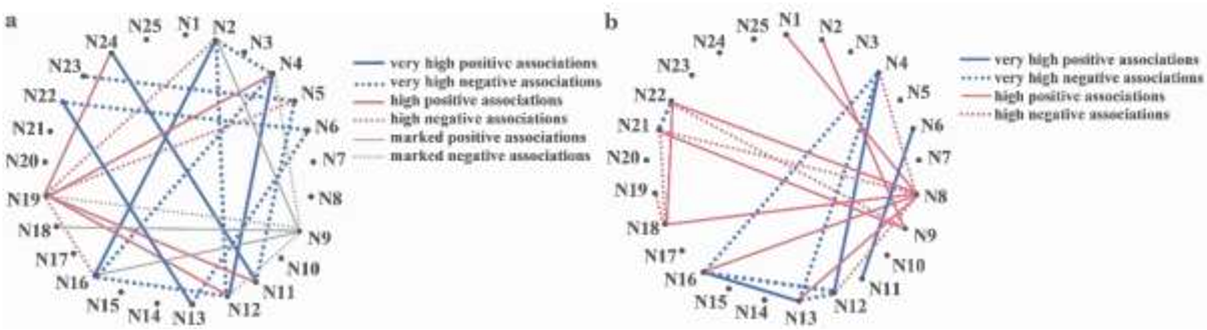
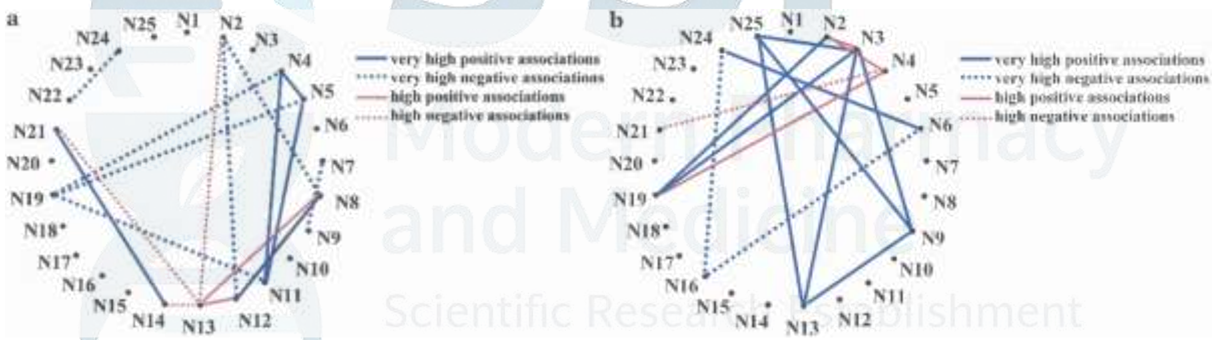


Fig. 8. Correlation portrait of the follicular cell energy capability profile under the consumption of a low dose of organic (**a**) and inorganic (**b**) iodine in conditions of iodine deficiency.

Another factor in the energy impact on the cell was the dose of iodine consumed (Figs. 9a, 9b, 9c) [39].

This was especially evident when inorganic iodine was taken. The architectonics of correlation portraits could be characterized by an insufficient number of connections between profile elements and a small number of connections at nodal dots, instability of the structure (due to an increase in the number of negative associations) or its balance, a small number of very high and high associations, or the prevalence of very high associations over high associations and positive associations over negative associations, or an even distribution of associations by strength and direction.



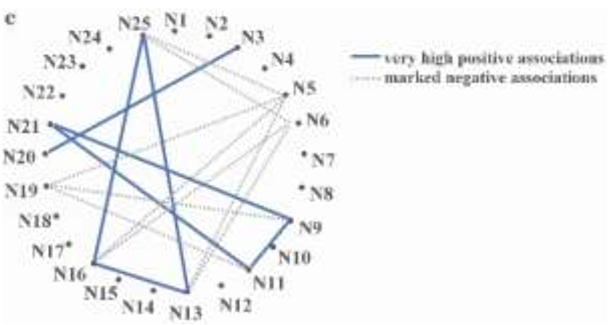


Fig. 9. Correlation portrait of the follicular cell energy capability profile under the consumption of a low dose (**a**), moderate dose (**b**), and high dose (**c**) of organic iodine in conditions of *Thiamazole*-potentiated iodine deficiency.

Under conditions of hyperthyroidism, the administration of exogenous thyroid hormone reduced the energy possibility of cells. This was indicated by fewer mitochondria, a homogeneous structure of their matrix, an indistinct contour of cristae, and disruption of the topographic connectivity between mitochondria and the rough ER and Golgi body. Iodine intake increased the energy possibility of follicular cells. This was evidenced by the involvement of most elements of the profile in the creation of correlation portraits and a decrease in the indicated morphological signs of functional stress of the follicular cell energy state. The analysis of the features of correlation portraits showed that when taking organic iodine, their structure was less rigid and more capable of change than when taking similar doses of inorganic iodine.

Currently, the study of the profile of morphofunctional basic capability of follicular cells is underway, in which the following integrative characteristics were chosen as the correct morphological structures: cell shape, condition of the lateral cell membranes, presence/absence of degeneratively altered cell membranes, nucleus shape, condition of the nuclear envelope, and chromatin.

Conclusions. By using correlation portraits, we made it possible to perform a comparative analysis of the effect of iodine of different chemical natures on the research aspects of follicular cell activity. To summarize the study of the organelle-cell level of thyroid integration into the whole-organism system, we emphasize the fundamental scientific value of the data obtained by analyzing the features of correlation portraits of the profiles of certain capabilities of follicular cells. The establishment of correlation portraits for research of the activity of hormone-producing cells made it possible to determine that the implementation of different directions of their activity is possible only under the conditions of simultaneous participation of all ultrastructures of one cluster (direction of activity). At the same time, the involvement of certain ultrastructures of one cluster depends on such factors as the thyroid functional state, the chemical nature of the iodine consumed, and the dose of iodine. The detected interchangeability and complementarity of structures of the same activity direction are a universal compensatory and adaptive mechanism that allows the follicular cell to respond adequately to changes in vital conditions. We consider it important to grade the qualities of the morphofunctional states of each structural element in the categories of "few – moderate – many" with the subsequent search for connections and dependencies between the number, structural features, state, and location of the elements of the research capabilities in the cell, and to determine harmonious or non-harmonious relationships between them.

The obtained results have a significant scientific novelty, as well as confirm, update, and extend the known data. The implementation of our multidisciplinary innovative approach based on mathematical methods to the research of the effect of organic and inorganic iodine on the morphofunctional state of cellular structures implementing different directions of thyroid hormone production proved the existence of differences in the effect of iodine of different chemical nature and established that they are based on the effect of different elements of the same structure or on the effect of different structures of the same hierarchical level.

The priority:

• A comparative research of the effect of organic and inorganic iodine on the peculiarities of thyroid hormone production on the organelle-cell level integration of the thyroid gland into the integral system of the body was accomplished, which allows to improve knowledge about the thyroid gland activity in normal and pathological conditions, expand the range of methods for its research, and conduct a selective approach to the selection of adequate iodine-containing compounds for correction of the body condition.

• A comprehensive package of mathematical approaches to the study of the follicular cell as the basis of the organelle-cell level of the structural organization of the thyroid gland with consistent application of the principle of clustering and Pearson's correlation analysis, the principles of phase interval and fuzzy logic, and mathematical statistics was suggested and tested, which leads to the further objectification of the results.

• The author's methods of semi-quantitative analysis of electronograms and determination of hormonopoietic cells' special capabilities profiles were tested, which are used to quantify cellular components in the areas of specialization, followed by the transformation of qualitative and binary indicators into quantitative ones by digital evaluation, which makes it possible to research the underlying mechanisms of thyroid hormone production while taking organic and inorganic iodine under conditions of different functional activity of the thyroid gland.

• The use of Pearson's correlation analysis to create correlation portraits of the profiles of synthetic, secretory, transport and energy capabilities of follicular cells allowed us to trace the links between the elements of the profiles in different states of the thyroid gland, which allows us to research their interdependence in more depth, characterize each of the directions of activity, and better understand their features under the influence of factors of different nature.

• The conceptual tools for studying correlation portraits of profiles of special capabilities of hormone-producing cells was developed and tested, which provides the identification of profile elements that are functionally significant for the implementation of the researched direction and common to all correlation portraits ("basic features"), the establishment of features individual to each correlation portrait ("actual features") and their "nodal dots" as clusters of correlations. This allowed us to individualize and generalize the findings of the research, to expand the area of search for regularities in the activity of the cell, indicated by the interconnections and interdependencies between the elements in the studied profiles.

• It was proposed to use complex morphofunctional markers for in-depth research of the synthetic activity of the "follicular cell system", which at the initial stages are changes in the number of free ribosomes and polysomes and the state of the structures of the rough endoplasmic reticulum ("markers of primary changes"), and at the final stages – changes in the number of fixed ribosomes and polysomes and the state of the components of Golgi body ("markers of final changes"), which deepens knowledge of morphofunctional changes in follicular cells at different stages of thyroid hormone production and expands the understanding of the activity of hormone-producing cells.

• It was established the concept of an "irritating dose" (minimally effective dose) of iodine as one that changes the morphological state of the elements of the profile of the research possibility and the correlations between them with the probable breakdown of adaptive mechanisms and disorders of hormone production, which allows to choose the chemical nature and dose of an iodine-containing drug to correct hypo- and hyperthyroidism by the functional state of the follicular cell.

It was approved:

• informative value of the linguistic characteristic of the results of electron microscopic examination of thyroid tissue in prepathological and pathological conditions;

• difference in the realization of protein synthesizing function by the rough endoplasmic reticulum and the Golgi body.

The proposed multidisciplinary innovative approach can be used for the research of other organs of the endocrine system.

Conflicts of interest. The funders had no role in the design of the study; in the collection, analysis, or interpretation of data; in the writing of the manuscript, or in the decision to publish the results. The author also states that he doesn't have any conflict or potential conflict of interest.

Ethical approval. The Bioethics Committee of the Private Higher Educational Institution "Lviv Medical University" approved the experimental design. All procedures complied with the requirements of the Law of Ukraine "On the Protection of Animals from Cruelty" (No. 3447-IV of February 21, 2006, as amended), as well as the provisions of the "European Convention for the Protection of Vertebrate Animals Used for Experimental and Other Scientific Purposes" (Strasbourg, 1986).

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