

IMPORTANCE OF SELENOPROTEINS FOR THE FUNCTION OF THE THYROID GLAND

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ABSTRACT

The trace element selenium (Se) influences many actions of endocrine system modifying expression of selenoproteins: glutathione peroxidases, thyoredoxin reductases and iodothyronin deiodinases. These enzymes participate in cellular processes acting as antioxidants, and modulating redox status and metabolism of thyroid hormones.

The thyroid gland contains as much Se per gram of tissue, as any organ. Selenium and iodine are essential for normal thyroid gland function and thyroid hormones homeostasis.

This study presents participation of selenoproteins in synthesis and control of thyroid hormones action and influence of different selenium intake on functional state of thyroid gland.

Keywords: selenoproteins, thyroid hormones, synthesis, action

Selenium (Se) is a co-factor of selenoproteins – the enzymes that participate in antioxidative defense of the organism, give assistance to apoptosis of neoplastic cells, improve immunologic response to infection diseases, suppress synthesis of prostaglandins, and assure maturity and normal maturation of spermatozoa. Selenium is important and for processes of cellular growth and modulation of action of transcriptional factors and cell-signaling systems. Biological role of selenium includes prevention from cancer (6, 11, 14), cardiovascular diseases (23, 24), viral mutations (2). It is responsible for optimal endocrine function and modulation of inflammatory response (1, 3, 20).

Selenium is essential trace element for all known forms of life. It is component of unique amino acid selenocystein. The first understanding for physiological importance of Se for nutrition was discovered in 1973, when it was described that Se has been essential component of some mammalian enzymes, such as glutathione peroxidases. The importance of selenium for human health was discovered in 1979, when Chinese scientists proved a statement true that the children lived at areas of selenium deficiency suffered from cardiomyopathy, known as Keshan disease, and symptoms of this disease were reversible after selenium supplementation. Extension of research work on the role of selenium for human organism leads to origination of advisable daily requirements of Se intake by World health organization in 1989 (21).

Selenium enters organism mainly by food. It was established that a diet containing 0.1 µg Se/g of food was enough for normal growth and reproduction for all mammalian organisms (26).

The main biological form of selenium is selenocystein (Sec), analog of cystein that is synthesized from a serin, bound to tRNA. selenocystein is identical with cystein, except the fact that instead of sulfur, it contains selenium atom that is ionized under physiological pH. Replacements of selenocystein by cystein into selenoproteins results of dramatically decrease of enzyme activity. This shows that Se atom is crucial for proper protein function (10, 21).

More than 25 selenoproteins are described in humans, the most of them have enzyme activity. They are divided into three families: glutathione peroxidases, thyoredoxin reductases, and iodothyronin deiodinases (19, 21,). All selenoproteins contain one or more selenocystein residues in primary structure. All selenoproteins, except one have enzyme activity, because selenocystein residues are situated at catalytic site, where they participate in redox reactions. Sequence of amino-acids, different expression in the tissues, and the other molecular properties of different family members vary in high degree. Under physiological conditions these enzymes perform metabolic and physiologic functions as: antioxidant defense, fertility, development and functioning of muscles, metabolism of thyroid hormones, and immunity.

Glutathione peroxidases (GPx) in humans are the family of close related antioxidant enzymes, coded by genes from GPX1 to GPX6. Cytosolic GPx1 is the most powerful antioxidant enzyme of this family. It is expressed by all cells of the organism and catalyzes reduction of hydrogen peroxide (H_2O_2) and the other organic peroxides. The other Glutathione peroxidases expressed in the thyroid gland are GPx3 and GPx4. GPx3 is an enzyme with extracellular action. GPx4 is called phospholipids hydroxiperoxidase, because it reduces phospholipids and cholesterol hydroperoxides, and it participates in shaping, and apoptosis of the cells (17, 18, 21).

Three thyroedoxin reductases (TrxR) are established. They catalyze NADPH-dependent reduction of oxidized thyroedoxin that participates in different redox systems (ribonucleotide reductase - essential for DNA synthesis, control of transcriptional factors, and processes of cell growth) (7).

There are three isoforms of iodothyronine deiodinases (5):

Type 1 deiodinase (D1) is cytosolic and membrane enzyme that is expressed in thyroid gland, liver, kidney and hypophysis. It transforms thyroid pro-hormone thyroxine (T_4) into active hormone tri-iodothyronine (T_3), catalyzing elimination of iodine from T_4 .

Type 2 deiodinase (D2) is an enzyme situated in endoplasmic reticulum and cellular membrane that is expressed in thyroid gland, brain, heart, gats and skeletal muscles. Its function is the same as the function of D1.

Type 3 deiodinase (D3) is present in cytosol and cellular membranes of the cells of the brain, placenta and skeletal muscles. It transforms T_3 into inactive rT_3 , catalyzing elimination of iodine from T_3 .

Regulation of selenoprotein synthesis depends on daily selenium intake that influences stability of mRNA. Under low Se content diet, GPx1 levels dramatically decrease. It is explained as the result of concomitant loss of proteins that correlates with loss of mRNA. Selenium supplementation increases selenoprotein synthesis because of increased levels of Sec-tRNA, leading to more efficient selenocystein incorporation (10).

The importance of selenium for endocrine system functioning is underlined by the fact that the most of endocrine cells have the mechanism to support relatively high concentrations of Se under conditions of heavy deficit of this trace element in the diet. They are well adapted to maintain selenoproteins expression of deiodinases, GPx4 and thyroedoxin reductases during selenium deficiency with distinction of GPx1 that is rapidly lost. Under insufficient selenium intake redistributing changes occur, because of mobilization of se from GPx stores of the liver, muscles, skin, and the other tissues and guidance of selenium to the brain, endocrine glands and reproductive organs (3,4).

The trace element selenium has possibility to influence many actions of endocrine system, modifying expression of selenoproteins that influence cellular processes acting as antioxidants, and as modulator of redox status and metabolism of thyroid hormones.

The thyroid gland contains as much selenium per gram of tissue as the other organs of the body have. Selenium and iodine are essential for normal function of the thyroid gland and homeostasis of thyroid hormones. Synthesis of the thyroid hormones requires iodination of tyrosyl residues on thyroglobulin that is stored into the thyroid follicle lumen. This reaction is catalyzed by thyroid peroxidase (TPx) and it requires the generation of high quantity of hydrogen peroxide which is harmful to the thyrocyte. Production of H_2O_2 appears to be the limiting step in thyroid hormone synthesis. It is controlled by the action of thyroid-stimulating hormone (TSH) using the complex of network of second messenger systems. Iodination of thyroglobulin and generation of H_2O_2 are performed on the luminal surface of the apical membrane of the thyrocytes. This organization of processes secures on one hand hydrogen peroxide for use in reactions of iodination, and on the other hand possibility to degrade diffused molecules of H_2O_2 into the thyrocyte by the intracellular GPx, TrxR and catalase.

The changes that occur in selenoprotein expression in the thyrocytes, stimulated by the TSH are:

- Activation of calcium-phosphoinositol signaling pathway
- Stimulation of production of H_2O_2
- Stimulation of expression of GPx1 and TrxR1
- Inhibition of GPx3 secretion
- Expression of GPx4 is not influenced by TSH stimulation.

These changes increase antioxidant cellular defense to prevent cells against the damage by the hydrogen and lipid hydroperoxides that may diffuse into the thyrocytes. The system of cAMP pathway stimulates expression of $\Delta 1$ and $\Delta 2$ in humans (in rats only - $\Delta 1$), and thus ensures deiodination of T_4 to T_3 .

At the basal states GPx3 is secreted actively into the follicular lumen and decreases hormone synthesis decreasing generated H_2O_2 (“down-regulation”). Expression of GPx1, TrxR1, and $\Delta 1$ is suppressed at the basal state. Glutathione peroxidase-3 is a potential regulator of thyroid hormone production, because of controlling action on the availability of H_2O_2 into the follicle.

Thyrocytes are permanently exposed to potentially toxic concentrations of hydro peroxides. Cytotoxic effect of H_2O_2 includes caspase-3-dependent apoptosis that occurs under H_2O_2 concentrations insufficient to induce necrosis. apoptotic response to H_2O_2 increases under selenium deficient state (9, 16). When the selenium intake is adequate, intracellular enzymes GPx and TrxR protect thyrocytes against peroxidative damage.

During iodine deficiency or hyperthyroidism, because of hyper stimulation of TSH-receptors of the thyrocytes, H_2O_2 production increases. because of activation of calcium-phosphoinositol system, stimulation of GPx1 and TrxR1 activity occurs ensuring “up-regulation” of antioxidant defense.

Selenium is regulator of T_3 production trough modulation of deiodinases expression. deiodinases control individual exposition of the different tissues to T_3 changing the rate of their expression.

Deiodinase $\Delta 1$ is the main form of this enzymes family. It catalyses 5 or 5`-mono deiodination and thus it converts T_4 to inactive rT_3 or active T_3 isomer. The most important physiological role of $\Delta 1$ is ensuring of normal plasma level of T_3 , and breakdown of rT_3 and T_3 -sulfate.

There are differences in expression of $\Delta 2$ between humans and the other mammalian species. In the rats $\Delta 2$ is mainly expressed in the brain, brown fat tissue, and hypophysis while it has lower expression or it miss in thyroid gland, skeletal muscles, and heart. Immunochemical studies showed that in humans $\Delta 2$ is expressed in thyroid gland, heart, brain, spinal cord, skeletal muscles, placenta, hypophysis and ceratocytes, and it has low expression in kidney and pancreas. deiodinase D2 can only change the reaction of 5`- deiodination and it has short half life (less than one hour). Physiologically $\Delta 2$ secures the level of intracellular entering of T_3 in specific tissues, but can influence also and the plasma level of T_3 . deiodinase D2 is important for regulation of brain development, THS secretion, and adaptive termogenesis in brown fat tissue, because of its physiological role (5, 18).

Selenium deficiency may influence function of the thyroid gland and metabolism of thyroid hormones. $\Delta 1$ of the liver ensures normal level of T_3 in circulation in rats with adequate selenium intake. Expression of $\Delta 1$ in the liver of the animals with selenium deficiency decreases with average 10%. Maintenance of plasma level of T_3 is performed by the adaptive answer of stimulated TSH secretion that allows increasing of thyroid hormone production. In humans $\Delta 2$ of thyroid gland also participates in maintenance of T_3 plasma level during conditions of selenium deficiency. Paradoxal increase of $\Delta 1$ in thyroid gland, found in rats with selenium deficiency, is due to retention of adequate quantity of this trace element by the gland under Se deficient diet (4). Because

$\mu 2$ expression and production of T_3 are vital important for control of termogenesis by brown fat tissue, the animals with selenium deficiency showed lower expression of $\mu 2$ and shorter survival under conditions of could stress than those with normal selenium intake. Myopathy and cardiomyopathy are close related with insufficient activity of T_3 in target cells, because of low deiodinases expression (15,18).

Experimental data were published that weanling rats slowed down the rate of growing after applied low Se diet. The rats receiving this diet had retardation of growth than those receiving diet with Se concentration 0.1 $\mu\text{g Se/g}$ of food and those with diet 0.2 $\mu\text{g Se/g}$ of food. The altered ratio between T_3 and T_4 plasma concentrations was obtained. The treatment with T_3 did not improve the rate of growing, whereas the treatment with selenium did (25). There are the evidence that low T_3/T_4 ratio in the elderly healthy subjects is related to impaired selenium status (22).

The habitants of selenium poor areas suffer more often from cretinism, cardiovascular, degenerative, and neoplastic diseases, than the other humans (6, 8, 18).

Deficit of Se into thyrocytes leads to decreased antioxidant state, apoptosis, increased exposition to harmful epitops that are recognized by the immune system and result in development of hypothyroidism (8, 9, 22). Selenium supplementation used to patients with autoimmune thyroiditis during three months at dosage 200 $\mu\text{g Se}$ / daily decreases significantly the plasma concentration of antibodies (12,13).

Selenium deficiency and increased TSH secretion may lead to development of necrosis that may cause fibrosis of the thyroid gland. Low plasma concentration of Se has strong relation with thyroid cancer development (18).

Despite of presence of developed mechanisms that permit accumulation of selenium in endocrine glands during selenium insufficiency situations, real possibility exists for disturbance of life important processes, because of low selenoproteins expression.

It is necessary to optimize and monitor selenium nutritional status for having a good health.

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