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**Research Article**

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# The Role of Thiamine in the Development of Wernicke Encephalopathy

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**RELEVANCE** Wernicke encephalopathy (WE) is an acute life-threatening neurological disease caused by thiamine deficiency. Vitamin B1 is a coenzyme that is involved in the process of maintaining the integrity of cell membranes, and, consequently, the normal functioning of the nervous system, muscles and heart. The prevalence of WE in the population is 0.4–2.8%. In the absence of timely treatment, WE leads to the development of severe disability, and in 20% of cases — to death.

**AIM OF STUDY** Systematization of data on the role of thiamine in the development of Wernicke encephalopathy.

**MATERIAL AND METHODS** To achieve this goal, the results of scientific research on WE were analyzed. The literature search was carried out in Scopus, eLibrary, PubMed electronic search engines using the following keywords: Wernicke encephalopathy, thiamine, alcohol abuse, thiamine deficiency. Scientific articles published between 1881 and 2024 were selected for analysis.

**RESULTS** The most common cause of WE is chronic alcoholism, which accounts for 50% of all cases. However, there are many other diseases and conditions that can lead to the development of WE. Vitamin B1 deficiency plays an important role in the development of WE.

**CONCLUSIONS** Vitamin B1 deficiency can develop as a result of a malfunction at various stages of the metabolic chain, during various pathological processes in the human body. Wernicke encephalopathy occurs not only in people who abuse alcohol, but also in pregnant women, cancer patients, patients with diseases of the gastrointestinal tract, liver and thyroid gland, after bariatric and other abdominal surgeries, as well as in patients on long-term parenteral nutrition. Thiamine deficiency, and, as a consequence, Wernicke encephalopathy, can lead to irreversible brain damage, severe disability and death.

**Keywords:** Wernicke encephalopathy; thiamine; alcohol abuse; thiamine deficiency; diseases of the gastrointestinal tract

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α-KGD — α-ketoglutarate dehydrogenase
AK — adenolate kinase
ATDP — adenosine thiamine diphosphate
ATP — adenosine triphosphate
ATTP — adenosine thiamine triphosphate
BBB — blood-brain barrier
CNS — central nervous system
CoA — coenzyme A
DNA — deoxyribonucleic acid
GIT — gastrointestinal tract
MATE — multidrug and toxin extrusion protein
NADP — nicotinamide adenine dinucleotide phosphate
PDH — pyruvate dehydrogenase
RNA — ribonucleic acid
TMP — thiamine monophosphate
TPP — thiamine pyrophosphate
TTP — thiamine triphosphate
WE — Wernicke encephalopathy

## INTRODUCTION

Wernicke encephalopathy (WE) is an acute life-threatening neurological disorder caused by a deficiency of thiamine (vitamin B1) [1]. Vitamin B1 is a coenzyme, involved in the process of maintaining the integrity of cell membranes, and, therefore, the normal functioning of the nervous system, muscles and heart. The half-life of thiamine is on average 2 weeks, its reserves in the body are limited, therefore, in the absence of vitamin B1 intake with food, deficiency symptoms appear after about 3 weeks [2].

WE was first described by Carl Wernicke in 1881 under the name of hemorrhagic encephalitis in two patients who abused alcohol, and one patient with pyloric stenosis due to the use of sulfuric acid [3]. The etiology of the disease was not established at that time, since the existence of vitamins was not yet known. It was not until 1912 that Casimir Funk isolated substances from raw white rice that he considered essential for life, and first called them "vitamins". Vitamin B1 was isolated by Barend Jansen and Willem Donath in 1926 [2, 4]. The relationship between thiamine and the development of WE was discovered even later – in 1941– by A.C.P. Campbell and R. Russell, who described 21 cases of the disease and suggested that the cause of WE development is a deficiency of vitamin B1 [5].

The prevalence of WE in the population is 0.4–2.8%. Men suffer from this disease more often, the incidence rate among women and men is 1:1.7. No racial predisposition to WE has been identified [6, 7]. The incidence of WE is higher in developing countries, which is associated with malnutrition and general vitamin deficiency [7]. Wernicke encephalopathy occurs not only in adults; cases of WE have also been described in children [8]. In the absence of timely treatment, WE leads to the development of severe disability, and in 20% of cases, to death [6].

**The aim of the study**: systematization of data on the role of thiamine in the development of WE.

## MATERIAL AND METHODS

To achieve the stated goal, the results of scientific studies devoted to WE were analyzed. The literature search was conducted in Scopus, eLibrary, PubMed electronic search engines using the keywords: Wernicke encephalopathy, thiamine, alcohol abuse, thiamine deficiency. Scientific articles published between 1881 and 2024 were selected for the analysis. 26% of the analyzed works devoted to the topic of WE were published no more than 5 years ago.

## RESULTS

### ETIOLOGY OF WERNICKE ENCEPHALOPATHY

The most common cause of WE is chronic alcoholism, which accounts for 50% of all cases [9]. However, there are many other diseases and conditions that can lead to WE development (Table 1) [9–11]. WE in childhood may be caused by inadequate thiamine intake due to maternal deficiency during breastfeeding or excessive dietary restrictions in conditions such as atopic dermatitis or gluten intolerance [9].

*Table 1*

**The mechanism of development of thiamine deficiency depending on the etiology of Wernicke encephalopathy**

| Causes | Mechanism of development of thiamine deficiency |
|---|---|
| Alcoholism | Decreased intake<br>Decreased intestinal absorption<br>Disruption of cellular metabolism<br>Decreased deposition<br>Excessive loss<br>Magnesium deficiency |
| Gastrointestinal diseases and surgeries | Decreased intake<br>Malabsorption in the intestine |
| Malnutrition (starvation, anorexia, unbalanced diet) | Decreased intake |
| Hyperemesis gravidarum | Decreased intake<br>Increased need and depletion of stores<br>Excessive loss |
| Oncological diseases | Decreased intake<br>Accelerated use<br>Inactivation of thiamine and enzymes of intermediate carbohydrate metabolism |
| Hyperthyroidism | Increased metabolism |
| Liver diseases | Decreased deposition |
| Chronic hemodialysis | Increased elimination |
| Parenteral nutrition | Insufficient or no intake |

### PATHOPHYSIOLOGY OF WERNICKE ENCEPHALOPATHY

Vitamin B1 deficiency plays an important role in WE development.

The causes of thiamine deficiency can be divided into 4 groups:

• decreased intake with food,
• impaired absorption,
• inability to convert thiamine into its biologically active form,
• excessive excretion [4].

The mechanism of development of thiamine deficiency depending on the main etiological factors of WE is presented in Table 1.

### THIAMINE INTAKE WITH FOOD

The recommended daily intake of thiamine depends on gender and caloric intake. Thiamine intake should be at least 0.4 mg/1000 kcal. The recommended daily intake of vitamin B1 with food is 1.4 mg for men and 1.0 mg for women. During pregnancy, the daily requirement for thiamine increases to 1.6–1.8 mg per day. If the daily intake of vitamin B1 is less than 0.2 mg/1000 kcal, its excretion in urine decreases [4]. Clinical symptoms of thiamine deficiency may appear within 8 weeks after a reduction in dietary intake [12].

Thiamine is found in many foods, including meat, whole grains, legumes, and some fruits (oranges, apples, etc.). Yeast extracts contain the most vitamin B1, while sugar lacks thiamine. In general, processed foods contain less thiamine than comparable unprocessed foods. Cooking foods can result in a loss of up to 20% of thiamine [13].

### THIAMINE COMPOUNDS

There are 6 known thiamine compounds:
1. free thiamine,
2. thiamine monophosphate (TMP),
3. thiamine pyrophosphate (TPP),
4. adenosine thiamine diphosphate (ATDP),
5. thiamine triphosphate (TTP)
6. adenosine thiamine triphosphate (ATTP) [14].

Free thiamine and TMP account for 5–15% of the total amount of vitamin B1. In the human body, 80–90% of thiamine is in the form of TPP, which is the main biologically active form and is present in high concentrations in skeletal muscles, liver, heart, kidneys, and brain. The remaining three compounds, ATDP, TTP and ATTP, account for only 1% of the total amount of vitamin B1 in the body [14].

Approximately 75% of whole blood thiamine is contained in red blood cells, 15% in white blood cells, and 10% in plasma [15]. Thiamine compounds can be phosphorylated or dephosphorylated as needed. The enzymes required for these processes are under genetic control (Table 2) [16–20].

*Table 2*

**Enzymes required for phosphorylation or dephosphorylation of thiamine compounds**

| Gene | Gene localization | Expressed transporter/enzyme | Reaction | Magnesium requirement | Pathology associated with genetic changes |
|---|---|---|---|---|---|
| Thiamine pyrophosphokinase 1 protein network | 7q35 | Thiamine diphospho-kinase/thiamine diphospho-transferase | Free thiamine → TPP | Best activation with $Mg^{2+}$ | Thiamine metabolism disorder syndrome 5: acute episodes of encephalopathy in early childhood |
| | | Thiamine difokinase | TPP → TTP | Not required | |
| AK1 | 9q34.11 | Erythrocyte adenylate kinase | TPP → TTP in erythrocytes | Required | Pathology associated with hemolytic anemia |
| Thiamine triphosphatase protein network | 14q11.2 | Thiamine triphosphatase/TTP hydrolase | TPP → TTP | Required | |
| Intestinal alkaline phosphatase | 2q27.1 1p36.12 | Alkaline phosphatase | TPP → TMP<br>TMP → free thiamine | As a cofactor in the intestine | |
| Multiple | Multiple | Acid phosphatase | TTP → TMP<br>TPP → TMP | As a cofactor | |
| Not established | Not established | Nucleoside triphosphate phosphatase/ non-specific diphosphate phosphohydrolase | TPP → TMP | Not required | |
| Not established | Not established | Thiamine phosphate (mono)-phosphatase | TMP → free thiamine | $Mg^{2+}$ increases membrane-bound activity by 1.7 times | |

Notes: AK — adenolate kinase; TMP — thiamine monophosphate; TPP — thiamine pyrophosphate; TTP — thiamine triphosphate

The function of free thiamine and TMP is to transport vitamin $B_1$ into and out of cells. Thiamine pyrophosphate and TTP are biologically active compounds. The different forms of thiamine are constantly converted into each other to ensure its availability [4].

## MECHANISM OF ACTION

Functions of thiamine:

1. coenzyme action – participation in energy metabolism,
2. non-coenzyme action – ensuring neurotransmission.

**Coenzyme action of thiamine**

Thiamine pyrophosphate (TPP) is an important cofactor in the metabolism of glucose, fatty acids, and proteins, as well as in the formation of adenosine triphosphate (ATP), namely: TPP is a critical cofactor for transketolase, pyruvate dehydrogenase (PDH), α-ketoglutarate dehydrogenase (α-KGD), α-keto acid dehydrogenase, and 2-hydroxyacyl-CoA lyase 1 (Table 3) [21]. These enzymes play a key role in the production of ATP by mitochondria, the synthesis of nucleic acids, and the metabolism of carbohydrates, fatty acids, and amino acids. When these enzymes

*Table 3*

**Key enzymes using thiamine pyrophosphate as a cofactor**

| Enzyme | Intracellular localization | Path/function | Magnesium as an additional cofactor | Functions of metabolic products | Consequences of deficiency |
|---|---|---|---|---|---|
| Transketolase | Cytosol, extracellular vesicles, nucleus, peroxisome | Pentose phosphate pathway | Yes | Substrates in glycolysis pathways; formation of d-ribose-5-phosphate → nucleotide synthesis → RNA/DNA synthesis; NADP as a reducing agent for fatty acid and acetylcholine synthesis, maintenance of myelin sheaths; synthesis of aromatic amino acids | ↓ energy supply of the cell; ↓ nucleotide synthesis; ↓ fatty acid synthesis → promotes demyelination; ↑ oxidative stress; amino acid imbalance |
| Transketolase protein 1 | Cytosol, nucleus | Pentose phosphate pathway | Yes | May modify the structure of TPP to alter its affinity for transketolase | Unknown |
| PDH | Mitochondria, nucleus | Glycolysis (rate-limiting cofactor) | Yes | Synthesis of fatty acids, ketone bodies and acetylcholine, maintenance of myelin sheaths; formation of acetyl-CoA; formation of citrate, the first component in the tricarboxylic acid cycle | ↓ fatty acid synthesis → demyelination; ↓ energy production (ATP) |
| α-KGD /oxoglutarate dehydrogenase complex | Mitochondria, nucleus | The tricarboxylic acid (citric acid) cycle | Yes | Energy production (ATP); formation of succinyl-CoA | ↑ nitric oxide and peroxidase activity → oxidative stress; ↓ energy production; lactic acidosis and и ↑ extracellular glutamate concentrations: → edema, → excitotoxicity, → ↑ BBB permeability, → neuronal death |
| branched-chain α-keto acid dehydrogenase | Mitochondria | Degradation of the branched chain amino acids valine, leucine and isoleucine, facilitating the oxidative decarboxylation step | Yes | Isobutyryl-CoA, α-methylbutyryl-CoA, isovaleryl-CoA → acetyl-CoA, acetoacetate, succinyl-CoA → fatty acids, synthesis of ketone bodies and acetylcholine, maintenance of myelin sheaths | ↓ fatty acid synthesis → demyelination; ↑ concentration of valine, leucine and isoleucine and corresponding α-keto acids |
| 2-Hydroxyacyl-CoA-lyase 1 | Cytosol, peroxisomes | Oxidation of fatty acids with 3-methyl branches such as phytanic and 2-hydroxy fatty acids (α-oxidation) | Yes | Formate → $CO_2$ | Defects in peroxisome biogenesis → disruption of the breakdown of certain nutrients, including amino acid degradation and β-oxidation of fatty acids |

Notes: α-KGD — α-ketoglutarate dehydrogenase; ATP — adenosine triphosphate; BBB — blood-brain barrier; DNA — deoxyribonucleic acid; CoA — coenzyme A; NADP — nicotinamide adenine dinucleotide phosphate; PDH — pyruvate dehydrogenase; RNA — ribonucleic acid; TPP — thiamine pyrophosphate

are impaired, energy metabolism is disrupted, oxidative stress increases, and undesirable metabolites may accumulate [17, 18, 21]. For example, when α-KGD function is impaired, glutamate is produced instead of succinyl-CoA, and when PDH function is impaired, lactate is produced instead of acetyl-CoA [21]. Thus, thiamine deficiency impairs energy metabolism and ATP production. Transketolase and α-KGD are key enzymes that utilize vitamin B1. Decreased α-KGD activity may occur within 4 days of the onset of thiamine deficiency and results in increased oxidative stress, lactic acidosis, excitotoxicity due to glutamate accumulation, inflammation and impairment of the blood-brain barrier (BBB) permeability, cerebral edema, and ultimately neuronal death. A decrease in transketolase may appear within 1 week after a decrease in vitamin B1 concentration [16].

**Non-coenzyme action of thiamine**

Thiamine phosphates act on neurotransmitters and hormones through second messengers. While other B vitamins activate the adenylate cyclase system, thiamine activates the guanylate cyclase system. Cyclic guanosine monophosphate is an important second messenger for peptide hormones and nitric oxide. By facilitating relaxation of smooth muscles, it regulates vascular and respiratory tone, intestinal peristalsis, and insulin secretion [22]. Thiamine pyrophosphate acts as a cofactor of PDH and promotes the synthesis of acetylcholine. However, thiamine also modulates choline neurotransmission non-enzymatically. This is supported by the fact that the metabolic antagonist of thiamine, oxythiamine, can increase the release of acetylcholine [23]. The role of TPP in modulating glutamate neurotransmission is due to its effect on α-KGD. In astrocytes, thiamine regulates the activity of glutamate and aspartate transporters, disruption of which can lead to insufficient excretion and intracellular accumulation of glutamate. Excessive glutamate content inside the cell leads to increased excitability, neurotoxicity and neuronal death [24].

## THIAMINE METABOLISM

**Transport of Vitamin $B_1$ into the Cell**

Thiamine plays a central role in many metabolic processes (Table 3), but is not synthesized intracellularly and enters the body only from the outside. In this regard, there are several thiamine transport systems that ensure its constant supply to the cell and mitochondria (Table 4). Depending on the actual plasma thiamine concentration, either reabsorption or excretion of vitamin B1 occurs in the kidneys. The functions of the transporters partially overlap: for example, the reduced folate carrier can intercept transport from the thiamine transporter 1. General cation transporters that are not specific for thiamine can also transport it in high concentrations. Such transporters include organic cation transporters and multidrug and toxin extrusion proteins (MATE) [14, 16, 18, 20, 25].

**Absorption of vitamin $B_1$ in the intestine**

Thiamine is found in food products mainly in phosphorylated forms. When ingested by the human body, thiamine is first dephosphorylated to the free form by gastrointestinal phosphatases [26]. Free thiamine is then absorbed in the small intestine, primarily in the jejunum. There are two mechanisms of vitamin B1 transport in the intestine: active and passive. The active transport system includes thiamine transporters 1 and 2 (Table 4) [27]. Passive transport is proportional to the concentration of thiamine in the intestinal lumen [28]. Since the vitamin B1 molecule is relatively large, its passive transport occurs in the form of facilitated diffusion along an electrochemical gradient through protein channels [29]. Active and passive transport of thiamine can occur simultaneously [30]. Active transport was shown to be necessary for maximal absorption of thiamine when its availability is low [31]. Animal experiments have shown that thiamine absorption in the small intestine can increase dramatically with its deficiency. However, with chronic alcohol consumption, thiamine absorption is reduced. In the presence of alcohol, the synthesis of thiamine transporters 1 and 2 is also significantly reduced [32].

In the enterocyte, as in any other cell, free thiamine can be phosphorylated directly to TPP: part of it is used by the enterocyte for its own metabolic needs, the rest of the TPP is broken down into TMP and free thiamine. Free thiamine and TMP are then transported from the cell into the plasma primarily by thiamine transporter 1, but other transporters may also be involved (Table 4) [27, 30]. Vitamin B1 can also be transported into the enterocyte by organic cation systems, from where organic cation carrier proteins 1 and 3 deliver thiamine into the blood [26, 30]. Transport of thiamine via the organic cation system is one of the mechanisms underlying

*Table 4*
**Thiamine transporters**

| Transporter | Action |
|---|---|
| Thiamine transporter 1 | High affinity carrier |
| Thiamine transporter 2 | High affinity carrier |
| Folate transporter/reduced folate carrier | May act as a transporter for TPP and/or TMP in some tissues when thiamine transporter 1 is not functional |
| Organic cation transporter 1 | Thiamine transport in the liver. Expressed in the renal tubules |
| Organic cation transporter 2 | Provides renal tubular secretion/reabsorption of thiamine. Expressed primarily in renal tubules, also in neurons and BBB vessels |
| Organic cation transporter 3 | Intestinal absorption and liver transport of thiamine. Expressed in BBB vessels and various brain regions, as well as in renal tubules |
| Mitochondrial TPF transporter | Mediates the entry of thiamine into the mitochondria. Important for brain development and affects the activity of α-KGD |
| Choline transporter-like protein | Acts as a carrier of TPP in the colon and promotes the absorption of thiamine produced by the microbiota (exists in the form of TPP) |
| MATE1 — multidrug and toxin extrusion protein | Secretion of thiamine by renal tubules. Expressed in renal tubules, BBB vessels |
| MATE2-K – a kidney-specific protein for multidrug and toxin extrusion | Secretion of thiamine by renal tubules. Expressed in renal tubules |

Notes: α-KGD — α-ketoglutarate dehydrogenase; BBB — blood-brain barrier; TMP — thiamine monophosphate; TPP — thiamine pyrophosphate; MATE — multi-antimicrobial extrusion protein

its passive transport at high concentrations. Alcohol disrupts the active intestinal transport mechanism of vitamin B1, but does not appear to affect the passive absorption of thiamine at high doses [28, 32].

### TRANSPORT OF THIAMINE INTO TISSUES

Once in the plasma, free thiamine and TMP are distributed throughout the body. Phosphorylated thiamine is partially bound to plasma proteins [33]. Free thiamine and TMP can penetrate into the cell: the former in the form of a cation passes through the cell membrane with the help of the thiamine transporter 1 (Table 4) [27]. The mechanism of TMP penetration through the cell membrane is carried out with the help of the reduced folate carrier, but it has not been fully studied [34]. In the cell, free thiamine is phosphorylated directly to TPP by the enzyme thiamine diphosphokinase without the formation of TMP as an intermediary: free thiamine + ATP → TPP + adenosine monophosphate. A small portion of vitamin B1 can be additionally phosphorylated to TTP, which can be dephosphorylated to TPP, TPP to TMP, and TMP to free thiamine [14]. Alcohol also has a direct effect on the processes of thiamine phosphorylation/dephosphorylation, reducing the concentration of the active form of thiamine.

About 2% of all available vitamin B1 is transported to the central nervous system (CNS) [32]. The anatomical structure of the BBB with tight junctions limits the ability of thiamine to enter the brain by simple passive diffusion - normally less than 10% of B vitamins enter the brain in this way [35]. The main amount of free thiamine enters the central nervous system via active transport involving the thiamine transporter 2 (Table 4). Vitamin B1 can also enter the brain using the reduced folate carrier [34].

The brain contains about 10 μmol of thiamine, and the metabolism rate is about 60-100% per day. Thus, homeostasis of vitamin B1 in the central nervous system is strictly regulated to ensure a stable balance between its intake and elimination [34]. McCandless D.W. et al. (1968) conducted an experiment on rats that were fed food with a deficiency of thiamine: the laboratory animals developed pronounced symptoms of encephalopathy with a decrease in the concentration of vitamin B1 in the brain to less than 20% of the norm. Increasing the concentration of thiamine in the CNS to only 26% of normal one resulted in almost complete restoration of neurological functions [36]. In humans, the reversibility of WE symptoms is variable. If treatment is started in a timely manner, regression of clinical and radiological manifestations may occur if irreversible damage and death of neurons has not taken place [37].

### VITAMIN $B_1$ RESERVES IN THE BODY

The thiamine reserve in the body is about 30 mg, most of it is contained intracellularly in the form of TPP [21]. In the highest concentrations, vitamin B1 is found in the heart, skin, kidneys, adipose tissue, lungs and colon [38]. There is little data on how long thiamine reserves are preserved in the body under

conditions of deficiency. For example, Ziporin Z.Z. et al. (1965) studied the excretion of thiamine in the urine of eight young men who consumed 10% of the recommended dietary intake of thiamine per day (2800 kcal, 400 g carbohydrates, 0.11–0.18 mg thiamine). Within 6 days, thiamine excretion in the subjects decreased to <50 μg/day, and on the 18th day, vitamin B1 was not detected in the urine [39]. A study by Ariaey-Nejad M.R. et al. (1970) involving three volunteers showed that the half-life of thiamine was 9.5, 13 and 18.5 days [40]. Thus, depletion of thiamine stores can occur within approximately 2–3 weeks after the onset of deficiency [4].

### THIAMINE INACTIVATION

Thiaminases I and II break down vitamin B1 into pyrimidine and thiazole moieties [41]. Normally, thiaminase activity in humans is insignificant. However, excessive consumption or improper processing of foods containing thiaminase may result in vitamin B1 deficiency. Type I thiaminase is found in fish, shellfish, ferns, and some bacteria. Thiaminase II is found in some bacteria [42]. Thiaminases are heat-stable but can be destroyed during cooking [21]. Thus, type I thiaminase, contained in the Australian fern, withstands the effects of high temperatures, but is destroyed by prolonged soaking in water. There is a known case of Europeans dying from beriberi due to thiaminase poisoning during an expedition to Australia in 1861: after the travelers ran out of meat, they ate flour based on fern leaves, preparing it differently from the indigenous people (it is suggested that the expedition members did not soak the Australian fern in water long enough to reduce the activity of thiaminase I) [42].

Polyhydroxyphenols, caffeic acid, phenols, flavonoids and tannins can also destroy vitamin B1. Thus, polyhydroxyphenols with antithiamine properties are found, for example, in coffee, tea, blueberries, black currants, Brussels sprouts and red cabbage. As a result of the oxidation process under the influence of polyhydroxyphenol, vitamin B1 is converted into thiamine disulfide, which is not absorbed in the intestine and, thus, becomes unsuitable for metabolism in the human body [43]. Polyhydroxyphenols are heat-stable and are not destroyed during cooking, so excessive consumption of foods containing them can lead to thiamine deficiency [21].

### ELIMINATION OF VITAMIN $B_1$

Up to 22 different thiamine metabolites were identified in the urine of rats [44]. The excretion and reabsorption of free thiamine by the kidneys can vary and largely depend on its current concentration in the blood plasma. Thiamine metabolites cannot be reabsorbed in the kidneys. Paradoxically, the amount of metabolites excreted in urine does not decrease even in thiamine deficiency [39].

In the renal glomeruli, thiamine, like any other small dissolved substance, is freely filtered. The filtered vitamin B1 is then processed in the proximal tubules. Thiamine stored in blood cells or bound to plasma proteins cannot be filtered. Under physiological conditions, up to 30% of plasma thiamine can be bound to albumin (10% TMP, 20% TPP) [33]. At thiamine concentrations greater than 119.5 μmol/l, its binding to plasma proteins decreases to 2% [4].

Under physiological conditions, thiamine is reabsorbed by the kidneys at concentrations up to 200 nmol/L to reduce excretion. Phosphorylated thiamine, mainly in the form of TMP, is dephosphorylated to free thiamine in the renal tubules [45]. Thiamine transporters 1 and 2 and organic cation transporter 1, expressed in the renal tubules, mediate the reabsorption of thiamine from urine by tubular cells. Thiamine transporter 1 and organic cation transporters 2 and 3 mediate the entry of thiamine from renal tubular cells into the blood. Thiamine transporters 1 and 2 have higher affinity than organic cation transporter 1 and provide for its reabsorption at lower concentrations. All thiamine transporters participate in both its reabsorption and excretion (Table 4) [25, 46]. Under conditions of deficiency, urinary thiamine excretion may decrease to undetectable levels [39].

When there is an excess of vitamin B1 in the body, for example, in the case of its injection, thiamine is completely excreted by the kidneys [45]. Elimination is enhanced by a switch from reabsorption to active secretion. In this case, thiamine that has not been filtered in the glomerulus is excreted through the renal tubular cells. Thiamine directly inhibits thiamine transporter 1-mediated reabsorption, which activates its secretion [47]. The kidneys can also remove thiamine via two types of cation

transporters: the organic cation transporter and the multidrug and toxin extrusion protein (MATE) (Table 4). Thiamine enters the renal tubular cells from the blood with the participation of organic cation transporters 1 and 2 [46]. Then, with the participation of the MATE1 and MATE2-K transporters, thiamine is excreted from the renal tubules into the urine [48]. With the help of this mechanism, complete elimination of thiamine from all blood plasma passing through the kidneys (renal blood flow) is possible. Elimination of vitamin B1 in this case is 5 times higher than the glomerular filtration rate [45].

### MAGNESIUM AS A THIAMINE COFACTOR

In the body, magnesium is found mainly as the divalent cation Mg2+. More than 99% of magnesium is found intracellularly [49].

Magnesium is required as a cofactor for the transport of thiamine and the conversion of various thiamine compounds into each other (Table 3). Without magnesium, thiamine cannot function properly. Thus, magnesium deficiency may reduce thiamine activity. However, it has not been established how significant the magnesium deficiency must be to cause clinical symptoms of thiamine deficiency [4].

The daily requirement for magnesium, according to various sources, ranges from 300 to 420 mg for men and 270–320 mg for women. During pregnancy, additional magnesium intake is not necessary. But nursing mothers need an additional 50 mg of magnesium per day to compensate for its loss with breast milk. Magnesium is found in almost all foods. Leafy vegetables contain especially large amounts of magnesium, which is the main component of chlorophyll. Whole grain cereals, nuts and yeast extracts are also rich sources of magnesium [13]. It should be taken into account that in the gastrointestinal tract, magnesium and calcium ions cause thiamine to become insoluble, sharply reducing its absorption, which requires their separate use whenever possible.

The normal serum magnesium concentration is in the range of 0.7 to 1.0 mmol/L. Magnesium deficiency can occur when its concentration in the blood serum falls below 0.66 mmol/L. However, clinical symptoms may only appear at levels below 0.5 mmol/L [50]. Since more than 99% of magnesium is found inside cells, its normal concentration in the blood serum does not exclude deficiency. This type of magnesium deficiency can occur in patients who have been abusing alcohol for a long time [51].

Magnesium deficiency can occur as a result of:

• decreased assimilation or absorption,

• increased excretion from the gastrointestinal tract or kidneys,

• transfer from the extracellular space to the intracellular space [52].

Decreased absorption of magnesium can occur both in general nutritional deficiencies and with the consumption of foods low in magnesium. Inflammatory bowel disease and treatment with proton pump inhibitors such as omeprazole reduce magnesium absorption. Increased loss of magnesium from the gastrointestinal tract occurs, for example, with excessive vomiting or laxative abuse. Renal loss of magnesium may occur in treatment with loop or thiazide diuretics, cisplatin, amphotericin, aminoglycosides, cyclosporine, and tacrolimus [52]. Increased excretion also takes place when tubular reabsorption is impaired as a result of kidney disease. Magnesium shifts from the extracellular to the intracellular space occurs in pancreatitis or during treatment for diabetic ketoacidosis or other metabolic acidosis. In chronic alcohol dependence, there are several risk factors for magnesium deficiency, including poor diet, altered gastrointestinal function due to proton pump inhibitor use and decreased absorption, increased diuresis, excessive urinary magnesium excretion, and vomiting [53].

### MECHANISMS OF THIAMINE DEFICIENCY DEVELOPMENT IN VARIOUS PATHOLOGICAL PROCESSES

Thiamine deficiency can develop in various pathological processes (Table 1), but is most often found in people who abuse alcohol.

Mechanisms of development of thiamine deficiency with alcohol consumption:

• decreased thiamine intake due to patients' refusal of vitamin-rich foods in favor of foods low in vitamins and high in carbohydrates;

• alcohol reduces the absorption of vitamin B1 in the intestine, including after a single dose;

• alcohol damages renal epithelial cells, which leads to increased loss of thiamine;

• in chronic alcoholic disease, the liver's ability to store vitamin B1 is reduced by 73%;

• alcohol reduces the activity of thiamine diphosphokinase, decreasing the amount of TPP available for use. And since the facilitated diffusion of thiamine into cells depends on the concentration gradient, low thiamine diphosphokinase activity further reduces the intracellular supply of vitamin $B_1$;

• Chronic alcohol consumption leads to magnesium deficiency, which is required as a cofactor for thiamine metabolism [54].

Thus, alcohol both directly and indirectly causes the development of thiamine deficiency.

Thiamine deficiency in patients with gastrointestinal diseases may be caused by malabsorption (in Crohn's disease) or insufficient intake of vitamin B1 and intractable vomiting (in intestinal obstruction) [9, 55]. Patients undergoing bariatric surgery are at risk of developing WE due to vitamin B1 deficiency caused by malnutrition, malabsorption, and vomiting [56]. Uncontrollable vomiting is also a cause of thiamine deficiency after gastrointestinal surgery and acute pancreatitis [55, 57, 58].

Oncological diseases, especially those accompanied by rapid cell growth (e.g., leukemia and lymphoma), lead to accelerated use of thiamine reserves [59, 60]. Insufficient vitamin B1 intake in malignant neoplasms can be a direct consequence of the disease and arise due to low appetite, or develop secondary to chemotherapy or vomiting. Some chemotherapeutic drugs, such as 5-fluorouracil and ifosfamide, inactivate thiamine and carbohydrate intermediate enzymes, leading to the development of cachexia [61].

Hyperthyroidism causes thiamine deficiency due to hypermetabolism, which leads to an increased need for vitamin B1 [11]. Chronic hemodialysis may result in increased excretion of thiamine, as it is excreted into the dialysate [62]. No parenteral nutrition solutions contain vitamins and microelements. Therefore, patients on long-term parenteral nutrition may develop thiamine deficiency due to insufficient or complete absence of its intake [63]. With long-term (more than 5 days) and especially total parenteral nutrition, all patients require additional administration of vitamins and microelements, especially if they are initially deficient.

## CLINICAL MANIFESTATIONS OF WERNICKE ENCEPHALOPATHY AS A CONSEQUENCE OF THIAMINE DEFICIENCY

Thiamin deficiency in the brain leads to cytotoxic edema and an increase in the volume of astrocytes within 4 days. After 7–10 days, decreased transketolase activity causes endothelial cell dysfunction, nitric oxide production, and release of intracellular glutamate into the extracellular space. Thus, the disruption of osmotic gradients and the production of free radicals lead to vasogenic edema and disruption of the BBB permeability. After 14 days, neuronal DNA fragmentation and lactic acidosis cause irreversible structural damage and death of nerve cells [16]. The most vulnerable area of the brain in WE are the mammillary bodies, damage to which, according to Victor M. et al. (1989), was detected in 100% of cases [64]. The reason for this selective neurodegeneration of the mammillary bodies, as well as the tegmentum of midbrain and periaqueductal gray substance, is currently unknown [65].

As a result of vitamin B1 deficiency against the background of the above-described mechanisms of its development in various pathologies, WE is clinically manifested by a disorder of consciousness, oculomotor dysfunction, and ataxia. However, the classic triad of symptoms occurs in only 16% of cases, in 29% of patients two of the three symptoms are detected, in 37% one, and in 18% of cases none of these symptoms are diagnosed [66].

Rare manifestations of WE are hypothermia, less commonly hyperthermia, hearing loss up to deafness in the late stages of the disease, epileptic seizures, arterial hypotension, tachycardia, syncope, polyneuropathy [67].

Wernicke encephalopathy can lead to irreversible brain damage, severe disability, and in 15–20% of cases, death [68]. Wernicke encephalopathy is an acute stage of Wernicke-Korsakoff syndrome, in the chronic period of which Korsakoff syndrome develops. Korsakoff syndrome occurs more often in untreated patients with alcoholic WE and is caused by damage to the mammillary bodies and thalamus [67].

Korsakoff syndrome is characterized by the following clinical symptoms: antero- and retrograde amnesia, confabulations, executive function and emotional disorders [69].

The European Federation of Neurological Societies (2010) developed diagnostic criteria for WE of alcoholic genesis:

1. alcohol-related malnutrition,
2. oculomotor disturbances,
3. balance disorders,
4. impaired consciousness or moderate cognitive decline.

To verify the diagnosis of WE, two of the four criteria must be present. These criteria are also applicable for establishing the diagnosis of non-alcoholic WE. The sensitivity and specificity of these criteria for the diagnosis of WE, including in combination with Korsakoff syndrome, is 85% and 100%, respectively [70].

An important component of the complex treatment and prevention of WE development is vitamin therapy in combination with microelements. Prompt administration of thiamine is the mainstay of treatment for WE. Replenishment of magnesium deficiency, which is an important cofactor in vitamin B1 metabolism, is also necessary in patients with WE.

## CONCLUSION

Thiamine is a key cofactor of human energy metabolism and an important factor influencing neurotransmitter functions. The human body has limited thiamine reserves, and vitamin $B_1$ homeostasis depends on its intake with food. Wernicke encephalopathy is a life-threatening disease caused by acute or chronic thiamine deficiency. Vitamin B1 deficiency can develop as a result of failure at various stages of the metabolic chain, with various pathological processes in the human body. Wernicke encephalopathy occurs not only in people who abuse alcohol, but also in pregnant women, cancer patients, patients with gastrointestinal tract, liver and thyroid diseases, after bariatric and other abdominal surgeries, and in patients on long-term parenteral nutrition. Thiamine deficiency and the resulting Wernicke encephalopathy can lead to irreversible brain damage, severe disability and death. Preventive administration of thiamine in any clinical suspicion of Wernicke encephalopathy is the mainstay of pathophysiological treatment.

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