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North-Western Medical University named after I. I. Mechnikov, Saint-Petersburg, Russia.

Abstract.

It has long been known about the need for folic acid for the vital activity of both macro- and micro-organisms. It is necessary for the processes of methylation, nucleotide synthesis and also the formation of methionine and reducing the toxic effect of homocysteine. The addition of synthetic folic acid to the diet of pregnant women, as well as at the stage of pre-pregnancy preparation, significantly reduces the risks of fetal neural tube defects, heart defects, and possibly other organs and systems of the body. In addition, folic acid can help improve fertility potential. However, there is evidence of adverse effects of folic acid on the health of older adults (hiding B12-deficient status) and the offspring of mothers taking high doses prescribed by medical specialists like a risk of infectious-inflammatory and allergic diseases of the upper respiratory tract in children, eczema, also disorders of psychomotor development and insulin resistance. In 1980, the direct excitatory effect of folic acid on synaptic transmission in the central nervous system was proven. This is due to the molecular structure, it contains L-glutamate. Therefore, the aim of the work was trying to prove the existing correlation data on probable neuropathologies, including a reduced threshold of seizures, a high risk of epilepsy in a model of offspring of Wistar rats with an increased dosage of folate throughout gestation and including at the stage of pre-gravidar preparation. In the control group, the average clonus time was 1779.6 seconds, in the experimental group with a 1 mg/kg/diet dosage of 797.3 seconds, and in the second group with a 5 mg/kg/diet 439.7 seconds (p < 0.01). The results obtained of the difference in the convulsive threshold may be due to changes in synaptic density as a result of an excess of synthetic folic acid during the formation of NT and subsequently during the differentiation of nervous tissue in the central nervous system (in particular, in the 3rd trimester with a massive appearance of glutamatergic receptors), which can affect the processes of neurogenesis and the formation of neural networks.

Key words. Folic acid, surplus, seizure threshold, synaptic density, myoclonus, gestation.

Introduction.

Folic acid is an essential biologically active substance in a living organism, it provides the process of DNA replication and nucleotide synthesis. Since it is vital, it is used in metabolic processes not only by multicellular organisms, but also by microorganisms. One of the main pathways of its metabolism is methionine and homocysteine exchanges: a methylating agent, SAM (S-adenosine methionine), is formed, which is involved in the methylation of proteins, mediators, nucleotides, phospholipids, and hormones [1]. N 5, N 10-methylenetetrahydrofolate (MTHF) and N 10-formyltetrahydrofolate are directly involved in the biosynthesis of nucleotides de novo - in particular, the lack of these forms of folic acid can lead to severe neural tube defects as a result of the incorporation of uracil into DNA instead of thymine.

It has long been known about the positive effects of folic acid on intrauterine development of the fetus: reducing the risk of neural tube defects, as well as heart defects [2]. Embryonic cells and syncyiotrophoblast, symplastotrophoblast are extremely sensitive to folic acid deficiency, since this is a rapidly proliferating cell pool, folate deficiency leads to cell stress, since methylation processes are disrupted, incl. DNA, which can lead to the development of various kinds of anomalies of differentiation and proliferation of both embryonic axial primordia and already more differentiated tissues. Children whose mothers received folate during preconception preparation and during pregnancy (1 trimester) showed improvement in cognitive functions in the preschool and early school period [3].

The concentration of folic acid in maternal erythrocytes also correlates with the weight and height of newborns. In the group with a low content of folate in plasma and erythrocytes, the frequency of intrauterine growth retardation of the fetus is higher than in the normal content [4].

Lack of folate intake during pregnancy in the 1st, 2nd, and 3rd trimesters also correlates with an increased risk of autism spectrum disorders in children, as they have a reduced content of methylating agents and folic acid metabolites in their blood [5,6].

Hyperhomocysteinemia is associated with folic acid metabolism, and high blood levels of homocysteine are a proven risk factor for cardiovascular disease [7]. Homocysteine increases both with mutational changes in the genes MTHFR, DHFR (the most common 677С-> T), and with a lack of folic acid intake, for example, in countries where there are no mandatory fortification programs. However, the risk of arterial hypertension (AH) during pregnancy was not associated with mandatory folate support for mothers, but the risk of developing preeclampsia (PE) was higher in the group of pregnant women without folate support [8]. The polymorphism of the MTHFR gene associated with high levels of homocysteine also proved to be the cause of menstrual dysfunction. This was shown in the BioCycle Study, a prospective long-term study (2005-2007), which included 259 women with normal menstrual cycles. An increase in the concentration of homocysteine in the control group increased the risk of an anovulatory cycle (sporadic anovulation) by 33%. These indicators were associated with the lack of adequate folate support.

Thus, folates are not only an essential micronutrient, but also a drug for the prevention of a fairly wide range of diseases.

There are two mechanisms of folate absorption, saturable and non-saturable. The former is distributed in the upper small intestine and is sensitive to reduced forms of folate and especially to MTHF. When the critical level for this mechanism, 200 μg of folates, is exceeded, the activity of the carrier apparently
assigned to placebo or folic acid supplements, the estimated acid is unsafe for such patients [14].

Researchers was shown to increase the risk of recurrence of non-invasive malignant neoplasms.

anomalies is a recommendation to take up to 4000 micrograms of neural tube defects and other folate-dependent developmental protection and human welfare of the Russian Federation, the as well as the Federal Service for Supervision of Consumer Rights folates up to 5 mg per day, although in the EU and the USA, as well as the Federal Service for Supervision of Consumer Rights Protection and Human Welfare of the Russian Federation, the idea of TOV (tolerable upper intake level) (800-1000 mcg) has already been formed. In particular, pregnant women with an increased body mass index may be prescribed 1-2 tablets of 1 mg of folic acid per day due to overdiagnosis in terms of preventing B9 deficiency, hypertension, and PE. The high risk of neural tube defects and other folate-dependent developmental anomalies is a recommendation to take up to 4000 micrograms of folic acid per day at least 3 months before conception and up to 12 weeks of pregnancy. At the same time, 800 μg should come from multivitamin complexes, and the rest in the form of synthetic folic acid [12]. Additional intake of folic acid is also recommended with a rational and sufficient diet in micronutrient content [13].

However, it is known that an excess of folic acid in the postnatal period can increase the risk of manifestation and recurrence of malignant neoplasms.

In a Southern California RCT, among 643 men randomly assigned to placebo or folic acid supplements, the estimated probability of being diagnosed with prostate cancer over a 10-year period was 9.7% in the folic acid group and 3.3% in the placebo group. These results highlight the potential complex role of folic acid in prostate cancer [15].

A 2012 meta-analysis of ten RCTs showed a borderline significant increase in total cancer in the folic acid group compared with controls [16]. However, other studies have shown that folic acid supplementation has no significant effect on overall cancer incidence, colorectal cancer, prostate cancer, lung cancer, breast cancer, or hematologic malignancies, but reduces the risk of melanoma [17,18]. But, unfortunately, the criteria for statistical significance were not significant in these meta-analyses (p = 0.10; p = 0.23).

In older adults with low vitamin B12 levels, high serum folic acid levels have been associated with anemia and cognitive impairment. However, when vitamin B12 levels were normal, high serum folic acid levels were associated with protection against cognitive impairment [19,20].

High consumption of synthetic folic acids by women during pregnancy is one of the risk factors for infectious and inflammatory and allergic diseases of the upper respiratory tract in children, eczema, as well as impaired psychomotor development and insulin resistance. In addition, there is evidence of an increased risk of multiple pregnancy with the use of high doses of folic acid [21].

An Indian study confirms higher insulin resistance in children born to mothers with high gestational folic acid levels. It also showed that this association persists from childhood to adolescence. It also suggests that disruption of the maternal one-carbon pathway is associated with impaired fetal growth and cardiometabolic risks later in life [22].

Folic acid and its related compounds are based on dihydropteroic acid conjugated to L-glutamate, the latter being the major excitatory neurotransmitter in the brain, and the CNS excitatory nature of folic acid itself has been previously reported in vitro.

Synthetic folic acid in an unmetabolized inactive form can also enter the systemic circulation and be taken up by cells. As a result of activation of the non-saturable pathway, it accumulates in the blood. An excess of synthetic folic acid during the formation of NT and subsequently during differentiation of the nervous tissue in the CNS (in particular, in the 3rd trimester with the massive appearance of glutamatergic receptors) can affect the processes of neurogenesis and the formation of neural networks [24].

But still, there is evidence that the intake of physiological folic acid after the closure of the NT (after the first trimester) has a positive prospective effect on the cognitive functions of the offspring. At 7 years of age, children of mothers treated with folic acid had significantly higher scores than the placebo group in verbal reasoning based on the BSITD-III and WPPSI-III test systems [23].

The aim of the work was an attempt to prove the existing data on probable neuropathologies, incl. reduced seizure threshold, high risk of epilepsy in the offspring model of Wistar rats with an increased dosage of folate throughout the gestation period and incl. at the stage of pregravid preparation.

### Table 1. Attack onset time.

<table>
<thead>
<tr>
<th>Control group</th>
<th>Experienced group 1</th>
<th>Experienced group 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>1680 sec</td>
<td>730 sec</td>
<td>480 sec</td>
</tr>
<tr>
<td>1685 sec</td>
<td>858 sec</td>
<td>450 sec</td>
</tr>
<tr>
<td>1920 sec</td>
<td>911 sec</td>
<td>602 sec</td>
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<tr>
<td>1260 sec</td>
<td>510 sec</td>
<td>598 sec</td>
</tr>
<tr>
<td>1800 sec</td>
<td>830 sec</td>
<td>1020 sec</td>
</tr>
<tr>
<td>1823 sec</td>
<td>791 sec</td>
<td>420 sec</td>
</tr>
<tr>
<td>1903 sec</td>
<td>1200 sec</td>
<td>30 sec</td>
</tr>
<tr>
<td>1718 sec</td>
<td>401 sec</td>
<td>840 sec</td>
</tr>
<tr>
<td>2115 sec</td>
<td>285 sec</td>
<td>330 sec</td>
</tr>
<tr>
<td>2317 sec</td>
<td>396 sec</td>
<td>300 sec</td>
</tr>
<tr>
<td>1620 sec</td>
<td>333 sec</td>
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<td>720 sec</td>
<td>275 sec</td>
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<td>1205 sec</td>
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</tr>
<tr>
<td>1735 sec</td>
<td>1360 sec</td>
<td>305 sec</td>
</tr>
<tr>
<td>1915 sec</td>
<td>1435 sec</td>
<td>450 sec</td>
</tr>
<tr>
<td>Σ = 1779.6 sec</td>
<td>Σ = 797.26 sec</td>
<td>Σ = 439.67 sec</td>
</tr>
</tbody>
</table>
Materials and methods.

The experimental design was projected onto laboratory animals. We used Wistar rats for them. Kyoto. This breed is normotensive, with the absence of genetic polymorphism of the MTHFR, DHFR and other genes associated with the metabolism of folic acid in the body, which allowed us to exclude the risks of complicated gestation and the development of increased neurological symptoms or the development of other adverse conditions in the offspring. Experiments on rats were carried out in accordance with the "Principles for the Care of Laboratory Animals" (1996). Female and male Wistar rats (n=30) were housed individually in polypropylene cages. The females were divided into 3 groups: control, experimental group 1, and experimental group 2. The control group received a standard diet. At the stage of pre-gravid preparation and gestation, premium varieties of feed with a complete micronutrient composition, in particular, with a physiological dosage of vitamin B12, were used in order to exclude B12-deficient conditions that could affect the result due to the similarity of biochemical mechanisms in the macroorganism of folic acid and B12. The dosage of folic acid was 0.4 mg/kg per diet, the 1st experimental group was fed a diet with a dosage of 1 mg/kg per diet, and the 2nd experimental group 5 mg/kg per diet. Folic acid was administered orally in 1 ml of 10% sucrose solution. Female rats received folic acid at the stage of pregravid preparation (one week before mating) to form a pool in erythrocytes. Subsequently, females were mated with control males (1 female per 1 male) and the day the vaginal plug was detected was defined as fetal day. Pregnant females were kept in individual polypropylene cages. Throughout the gestation, the animals were on a given diet. Only after giving birth, the females were deprived of folate support, and folates were not fed to the offspring. The offspring were kept on a standard diet for a month until maturity. A month later, the ability for the first convulsive act was determined on the control males (1 female per 1 male) and the day the vaginal plug was detected was defined as fetal day. Pregnant females were housed individually in polypropylene cages. Throughout the gestation, the animals were on a given diet. Only after giving birth, the females were deprived of folate support, and folates were not fed to the offspring. The offspring were kept on a standard diet for a month until maturity. A month later, the ability for the first convulsive act was determined on the control males (1 female per 1 male) and the day the vaginal plug was detected was defined as fetal day. Pregnant females were housed individually in polypropylene cages. Throughout the gestation, the animals were on a given diet. 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