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Folate and homocysteine metabolisms and their roles in the biochemical basis of neuropsychiatry

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Abstract: The term 'one-carbon metabolism' is commonly used to describe 3 separate metabolic processes: folate metabolism, the homocysteine remethylation cycle, and the transsulfuration pathway. Folate metabolism concerns the biochemical reactions in which endogenous and exogenous one-carbon units are transferred to tetrahydrofolates. The remethylation cycle is used for the synthesis of methionine from homocysteine with one-carbon units that come from folate. This methionine is then used for the synthesis of S-adenosyl methionine, which is a general donor of methyl groups for many biochemical reactions in the human body. In the transsulfuration pathway, some amino acids and polypeptides, such as cystathionine, cysteine, and glutathione, are synthesized from homocysteine. The kinetics of the enzymes in this pathway are regulated by the substrates of the remethylation cycle. The methylation process has been thought to have an important role in the biochemical basis of neuropsychiatry. An elevated homocysteine level is the most important marker of folate and vitamin B_{12} deficiencies, and also the most reliable biochemical sign of functional insufficiency. Some neurological and neuropsychiatric diseases, such as psychosis, Alzheimer's disease, and autism, have been found to be related to disorders of one-carbon metabolism. This review aims to summarize both one-carbon metabolism and its relationships with neuropsychiatric disorders.

Key words: One-carbon metabolism, folic acid, folate subgroups, homocysteine, vitamin B_{12}, neuropsychiatric disorders

1. Introduction

When considering its relations with many biochemical reactions and its roles in some essential metabolisms, disorders or imbalances of the one-carbon metabolism may result in wide ranges of disorders that affect human health, particularly in neuropsychiatric and cardiovascular areas.

Folate metabolism is one of the basic metabolisms of biochemistry in which one-carbon units are transferred to homocysteine, as well as purine-pyrimidine nucleotides and some amino acids are synthesized. Homocysteine is a molecule that stands at the junction point of the remethylation cycle and the transsulfuration pathway.

Understanding biochemistry, regulations, and relationships of one-carbon metabolism could encourage researchers to investigate the neuropsychiatric disorders through performing advanced studies that produce valuable findings elucidating the causal and molecular basis of the pathogenesis.

Because they provide detoxification of homocysteine, the remethylation cycle and the transsulfuration pathway together can be evaluated as 'homocysteine metabolism'. Hence, one-carbon metabolism will be explained under 2 titles: folate and homocysteine metabolisms.

2. Folate and its metabolism

2.1. Folic acid

Folic acid is a water-soluble vitamin from the B group (vitamin B_9), which is also referred to as folate and pteroyl monoglutamate (PteGlu). Its chemical structure consists of 3 parts: a pteridine ring, paraaminobenzoic acid, and glutamic acid (Figure 1). Natural folates are classified according to the oxidation state of the pteridine ring, the nature of the one-carbon units at the N^5 and N^{10} positions, and the number of glutamic acid residues.

2.2. Dietary sources and absorption

Humans cannot synthesize folic acid and thus are dependent on dietary sources. Yeast extracts, liver, kidney, leafy green vegetables, and citrus fruits are folate-rich foods. Bread, potatoes, and dairy products are middle-grade sources, but because they are consumed in large quantities, they contribute significantly to total folate intake (1). Folates in foods are transported via an ion-exchange mechanism

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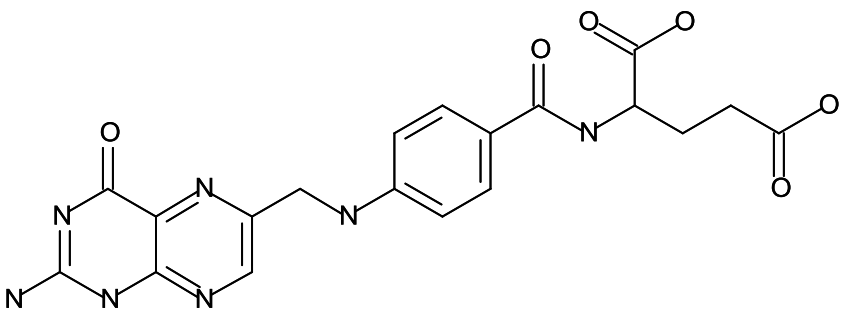

Figure 1. Chemical structure of folic acid.

that is carried out against the pH gradient along the brush membrane of enterocytes. Folate is anionic at intraluminal pH and it is exchanged with a hydroxyl anion. Although absorption is higher proximally, it is absorbed all along the jejunum. Polyglutamyl folates are hydrolyzed into monoglutamyl folates by gamma-glutamyl hydrolase (GGH) and then all monoglutamyl folates are converted into 5-methyltetrahydrofolate-monoglutamate (5-MTHF-Glu_1) in enterocytes. 5-MTHF-Glu_1 is the plasma form of this vitamin and it is transported to the peripheral tissues, where it is converted into tetrahydrofolate-monoglutamate (THF-Glu_1) via a reaction catalyzed by methionine synthase that uses vitamin B_{12} as a cofactor (2).

2.3. Folate transport

2.3.1. Transport in plasma

After absorption, 5-MTHF-Glu_1 enters the portal circulation. The liver takes up most of this folate and some of it is released into the enterohepatic cycle by secretion into the bile. The plasma concentration of 5-MTHF-Glu_1 is 3–30 ng/mL. In short-term folic acid deficiency, folylmonoglutamate pools in cells and the enterohepatic cycle maintain the plasma level. Decreased tissue folate intake leads to diminished cellular folylpolyglutamate synthesis and increased cellular transformation of folylpolyglutamate, by hydrolysis, into monoglutamate species. 5-MTHF-Glu_1 is reabsorbed from the renal proximal tubules via receptor-mediated endocytosis and contributes to plasma 5-MTHF-Glu_1 levels. Due to the GGH enzyme in plasma, folylpolyglutamate is not found in plasma (3).

Approximately 30%–40% of endogenous plasma folate is attached to low-affinity proteins, especially albumin; other proteins include alpha-2-macroglobulin and transferrin. In folate deficiency, the bound folate increases. Plasma also contains high-affinity folate-binding proteins in small amounts. Their amounts increase in folate deficiency, pregnancy, leukemia, and uremia. These proteins are found at high concentrations in blood obtained from the umbilical cord. The high-affinity folate-binding proteins in plasma are homologs of the folate-binding proteins found at the cell membrane (4).

2.3.2. Transport in erythrocytes

During erythropoiesis in the bone marrow, folate is found in growing erythroblasts. Most of the folate in erythrocytes is in the form of 5-MTHF-Glu_n and 5-formyltetrahydrofolate (5-FTHF)-Glu_n (5). The normal intraerythrocyte concentration is 190–650 ng/mL; in deficiency, it is 150–189 ng/mL; and in insufficiency, it is <150 ng/mL. There is no known role for erythrocyte folate, but it is thought that this folate is involved in long-term folate homeostasis and reserves. In contrast to plasma concentrations, it is not affected by recently eaten foods. Thus, measurement of erythrocyte folate can provide information about long-term folate status. Folic acid in old erythrocytes is rescued by the reticuloendothelial system and then transported to the liver.

2.3.3. Cellular and intracellular transport

In plasma, folate monoglutamates are present in a hydrophilic form with 2 valence anions at nanomolar concentrations (6). For this reason, there is a need for transport systems to operate against the more concentrated intracellular medium. Folate transport is also important for intracellular compartmentalization, not just at the cell membrane (7). There are 3 physiological mechanisms for transportation from the cell membrane. The first is transport by the folate-binding proteins/folate receptors (FRs) family, which moves folate into the cell unidirectionally (8). FRs operate by receptor-mediated endocytosis. They are held in the plasma membrane by a glycosylinositol anchor and are largely limited to the apical membrane of epithelial cells (9). They can bind various folyl coenzymes with high affinity. The protein–folate complex is taken inside the cell by a nonclathrin-mediated endocytotic pathway without lysosomal function (10).

Certain tissues are rich in the components of this transport system, such as the choroid plexus, vas deferens, renal proximal tubules, erythropoietic cells, ova, and placental trophoblasts (11). The second mechanism is transport via reduced folate carrier (RFC). Unlike receptor-mediated transport, this allows bidirectional transportation. The RFC serves as an anion exchanger that increases intracellular folate concentrations (5). This is the major folate uptake pathway in mammalian cells. In addition, this transporter-mediated system is found in other subcellular organelles, especially lysosomes and mitochondria (5). This transporter-mediated process is more effective than receptor-mediated transport (11). As a third mechanism, it has been shown that there can be folate transportation via passive diffusion across cell membranes (7).

Folate polyglutamate species with up to 4 glutamate residues can be ejected from the cell in 3 different ways: via multidrug resistance protein family members (MRPs/ABCCs), breast cancer resistance protein family members (BRCP/ABCG2), and RFCs. The first 2 are adenosine triphosphate (ATP)-dependent and downregulated in folate deficiency (12).

While folate transport to mitochondria occurs in monoglutamate form, transport outside of the mitochondria is carried out in both mono- and polyglutamate forms. Monoglutamates that enter mitochondria can be converted into polyglutamate forms by folylpolyglutamate synthase (FPGS). How polyglutamates leave mitochondria remains unclear (13).

Folate polyglutamates in the cytoplasm can enter lysosomes via a transporter-mediated system, and there they can be converted into monoglutamate forms, again by GGH. However, it remains unknown how monoglutamyl folates exit lysosomes and endosomes (13).

Folate enters a cell as 5-MTHF-Glu_1 on a large scale. In cells, the vitamin B_{12}-dependent methionine synthase acts as the rate-limiting step for the intracellular accumulation of folate. At the same time, transformation of 5-MTHF-Glu_1 into tetrahydrofolate by vitamin B_{12}-dependent methionine synthase leads to the transformation of dietary-origin 5-MTHFGlu_1 into the biologically more useful intracellular vitamin form, which can also be used in nucleotide biosynthesis. This reaction is a unique step, demethylating 5-MTHF-Glu_1 into THF-Glu_1 (13,14).

Folylpolyglutamates are generally better substrates than monoglutamyl forms for folate-dependent enzymes (15). Although the liver has the highest FPGS activity and is the main folate depot, folate polyglutamylation occurs in many different cell types. As oligo-gamma-glutamyl chain length rises, K_m values decrease. The oligo-gamma-glutamyl chain that can be conjugated to folate provides the cellular retention of folate, regulates the reaction rate, and facilitates the participation of substrate in the reaction (15). In mammalian cells, FPGS isoenzymes function in both the cytosol and mitochondria. While cytosolic FPGS is necessary to maintain the cytosolic folate pool, mitochondrial FPGS is essential for the accumulation of folate in mitochondria (16). Increased FPGS activity increases the chain length of folate polyglutamate; however, increased folate monoglutamate intake decreases it, because of substrate competition (17). Cellular retention of folate is also regulated by GGH. This enzyme lets folate-monoglutamates exit from the cell by separating polyglutamate peptides from polyglutamylfolates. GGH exists in many tissues, especially in lysosomes (13).

2.4. Intracellular distribution of folate

Most cellular folate is held in intracellular compartments. Almost half of it is located in mitochondria and a large part of the rest is in the cytoplasm. Although folate exists in other organelles, including the nucleus, these do not make an important contribution to total cellular folate concentrations (16).

Most cellular folate is attached to proteins. Approximately 60% of cytoplasmic folate and 20% of mitochondrial folate is tightly bound with proteins in rat liver. Studies on cell cultures have shown that unbound or free folate concentrations are negligible (18). The major proteins that tightly bind intracellular folate in rat liver include mitochondrial sarcosine and dimethylglycine dehydrogenase, cytoplasmic glycine-N-methyltransferase (19), and 10-formyltetrahydrofolate dehydrogenase. These proteins are synthesized in large amounts in the liver, which stores almost half of the total body folate (20).

Folate metabolism in cytoplasm is required for de novo purine and pyrimidine synthesis, and for the remethylation of homocysteine into methionine. In addition, mitochondrial folate metabolism provides one-carbon units for cytoplasmic one-carbon metabolism in the production of amino acids, as serine, glycine, sarcosine, and dimethylglycine. Folate metabolism in the nucleus is involved in the synthesis of dTMP and serine from dUMP.

3. Homocysteine and its metabolism

Homocysteine (2-amino-4-mercapto butyric acid) is a sulfur-containing amino acid from a nonprotein source; it is not included in the structure of any protein and is synthesized from methionine. Homocysteine is oxidized rapidly in plasma and thus it can be found in many forms. Most of it is bound to albumin with a disulfide bond. The rest is in unbound free disulfide and sulfhydryl forms (21). Homocysteine exists at the junction point of 2 important pathways and is regulated by many different enzymes (Figure 2). The destiny of homocysteine, between de novo methionine biosynthesis and the transsulfuration pathway, is determined by S-adenosylmethionine (SAM) allosterically (22).

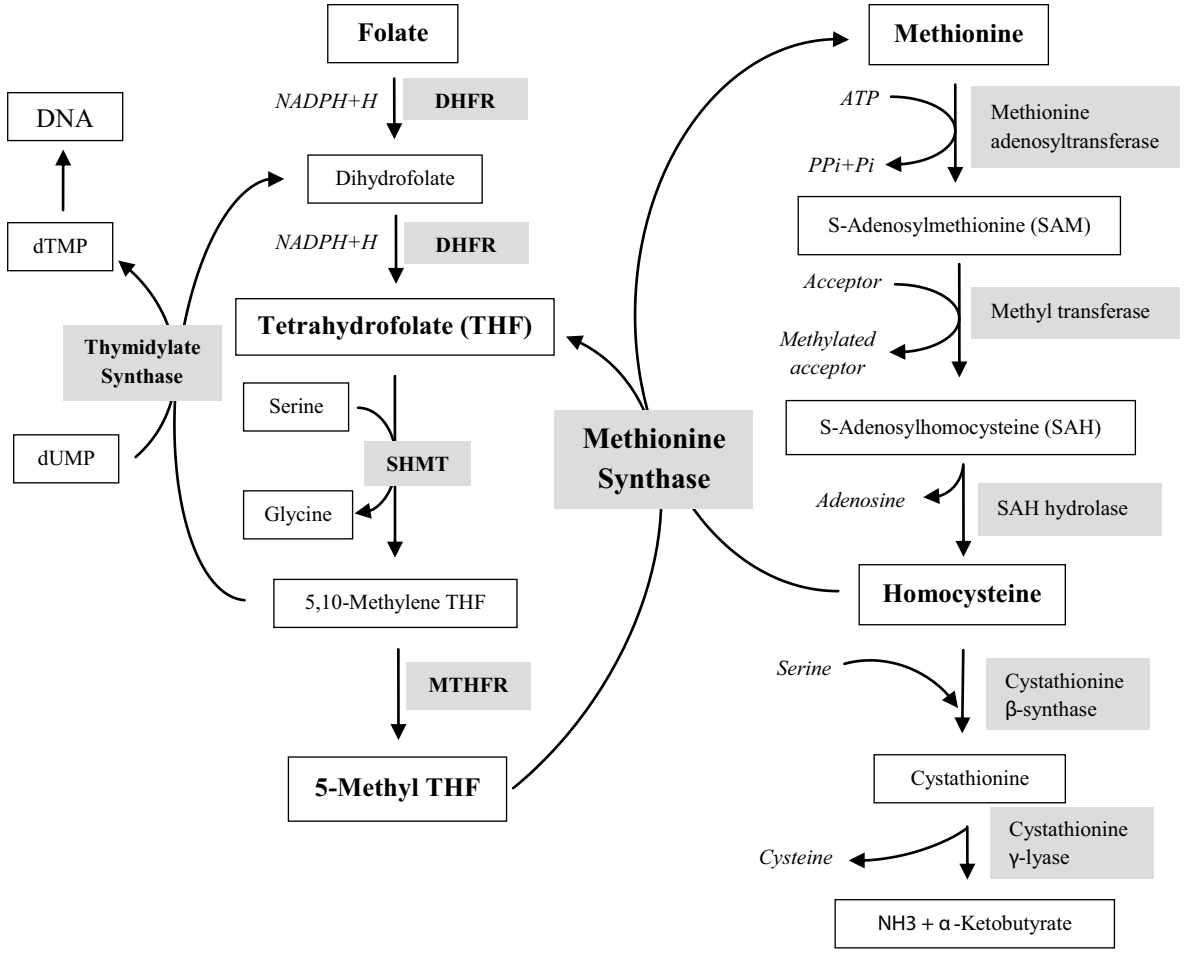

Figure 2. Folate and homocysteine metabolisms. DHFR, dihydrofolate reductase; SHMT, serine hydroxymethyl transferase; MTHFR, methylene tetrahydrofolate reductase.

In the homocysteine remethylation cycle, at the beginning, 5,10-methylene-THF is reduced to 5-MTHF by 5,10-methylene tetrahydrofolate reductase (MTHFR). This is a unique in vivo reaction that produces 5-MTHF. Vitamin B_{12}-dependent methionine synthase then converts the homocysteine into methionine; in this process, 5-MTHF is transformed into THF. This final step requires methionine synthase reductase (MSR), which activates the methionine synthase by reducing it. In addition, homocysteine can be converted into methionine by betaine-homocysteine methyltransferase (BHMT), which is not dependent on vitamin B_{12}. Subsequently, synthesized methionine is transformed into SAM, which is a general methyl donor for some important biomolecules, such as adrenaline, phosphatidylcholine, and carnitine, by methionine adenosyl transferase and ATP. The cycle is then completed with the transformation of SAM into S-adenosyl homocysteine (SAH), and later, back into homocysteine.

The transsulfuration of homocysteine involves uniting with serine to produce cystathionine. This vitamin B_6-dependent reaction is catalyzed by cystathionine-β-synthase (CBS). After passing this step, homocysteine can no longer be a precursor for methionine. Next, cystathionine is hydrolyzed into cysteine and α-ketobutyrate by another vitamin B_6-dependent enzyme, cystathionine-γ-lyase (CGL) (Figure 2).

In vitamin B_{12} functional deficiency, homocysteine and methylmalonic acid (MMA) levels increase in plasma and urine. Because folate is another coenzyme of methionine synthase, MMA measurements are more selective for vitamin B_{12} status alone (23).

4. Metabolic regulation of remethylation and transsulfuration pathways

The transfer of one-carbon units that have important roles in human biochemistry is executed generally with SAM, synthesized from methionine. Methionine is

supplied from exogenous sources, such as food, and from homocysteine in the remethylation cycle, where 5methyl THF and vitamin B_{12} are cofactors.

While SAM inhibits MTHFR, it activates CBS allosterically. For this reason, when SAM levels decrease, 5-MTHF synthesis will be limited and cystathionine formation will be reduced. In this case, homocysteine is cannibalized for methionine production. In the opposite condition, homocysteine is shifted to the transsulfuration pathway. SAH limits its own synthesis by inhibiting SAM-dependent methyltransferases, as well as by abolishing MTHFR inhibition by SAM. In addition, both SAH and methionine inhibit methionine synthase (22) (Table).

The SAM/SAH ratio, homocysteine concentration, specific dietary factors (especially folate and methionine), vitamin B_{12}, and vitamin B_6 are all important determinants of one-carbon metabolism and the metabolic balance between the remethylation and transsulfuration pathways (2). Humans consume many more methyl groups than are gained from dietary methionine. Betaine and 5-MTHF compensate for this deficit. The cause of the continuous SAM requirement is creatine formation, which consumes more SAM than other transmethylation reactions. In addition to the allosteric regulation of SAM, 5-MTHF also has effects on methionine metabolism. If SAM production from methyl groups from 5-MTHF is more than that from dietary methionine, excess 5-MTHF inhibits glycine-N-methyltransferase and thus SAM utilization (24).

5. Relationship between one-carbon metabolism and neurological and neuropsychiatric disorders

The methylation process may play a central role in the biochemical bases of neuropsychiatry. Folate and vitamin B_{12} are independent and essential components of one-carbon metabolism (25). Deficiency in vitamin B_{12}, which is also a cofactor for methionine synthase, also leads to a functional deficiency in folate and plays a role as another cofactor of the same enzyme. On the other hand, low folate concentrations cause reductions in neurotransmitter synthesis, SAM synthesis, and the methylation of phospholipids in neuronal membranes.

The most important result of these deficiencies, and also the most suitable biochemical sign of functional insufficiency of folate and vitamin B_{12}, is elevated homocysteine levels. Excess homocysteine released from extrahepatic tissues that do not have the transsulfuration pathway is taken up by the liver for remethylation into methionine; in cases of pathological accumulation of homocysteine, this can lead to homocysteinuria, or, in some cases, reduced urinary excretion of homocysteine. The nervous system is particularly sensitive to extracellular homocysteine. Indeed, homocysteine has

Table. Metabolic regulation of remethylation and transsulfuration pathways*.

Enzyme	K_m, μM	Intense tissues	Effects of metabolites		
			Methionine	SAM	SAH
MAT 1	3–41	L	S	P	
MAT 2	4–23	Extrahepatic	S	P, I	
SAHH	8–60	All tissues			S
MS	60	All tissues	P, I		I
MTHFR	---	All tissues		I	A
BHMT	2–60	L, K	P, I	InA, DR	I
MAT 3	30–1300	L	S	P, A	
CBS	1000-25,000	L, K, B, Pa, SI		A	A
CGL	3000	L, K, Pa, SI	I		
GNMT	30–180	L, K, Pa, SI		S, A	P, I

Abbreviations:
MAT: methionine adenosyl transferase, SAHH: S-adenosylhomocysteine hydrolase, MS: methionine synthase, MTHFR: methylene tetrahydrofolate reductase, BHMT: betaine hydroxymethyl transferase, CBS: cystathionine-β-synthase, CGL: cystathionine-γ-lyase, GNMT: glycine-N-methyl transferase.
L: liver, K: kidney, B: brain, Pa: pancreas, SI: small intestine.
S: substrate, P: product, I: inhibitor, A: activator, InA: inactivator, DR: down-regulator at synthesis.
* Sources of data detailed by Finkelstein (24).

neurotoxic and vasculotoxic effects (26–28), and is also a risk factor for atherosclerosis, atherothrombosis, and endothelial dysfunction (29,30). In fact, homocysteine can be transformed into cystathionine via cystathionine-β-synthase activity; as a result of this cystathionine-β-synthase action, the antioxidant glutathione can compensate for potential oxidative damage from excess homocysteine (31). Although there is no conversion of cystathionine into cysteine in the brain, the conversion of homocysteine into cystathionine does occur (32). Homocysteine causes synaptic dysfunction and neuronal damage as a result of metabolic effects (26,33,34), as follows.

- It is an agonist for NMDA calcium channels, causing excitotoxicity and damaging neuronal DNA.
- It can start calcium efflux by having direct effects on glutamate receptors.
- It can potentiate its own pathogenic effects by inducing stress in the endoplasmic reticulum.
- It induces oxidative stress, leading to the formation of reactive oxygen species.
- It can activate apoptotic signal cascades, such as P53 and Bax.
- It can cause cytochrome *c* release and caspase activation.

Fetuses of pregnant women with dietary folate deficiency are at risk for neural tube defects, such as spina bifida, meningocele, encephalocele, and anencephaly (35). Studies of cultured embryonic brain cells have shown that folate-deprived astrocytes and neural stem cells inhibit their own proliferations (33). In addition, methotrexate, an inhibitor of folate metabolism, inhibits neural progenitor cell proliferation and induces apoptosis in newly generated neurons (36). During the infancy period, vitamin B_{12} deficiency results in psychomotor regression, sensorial neuropathy, serious hypotonia, and apathy, all of which are associated with impaired myelination (37,38).

The most common polymorphism on the MTHFR gene is C677T. In homozygous individuals, there is mild homocysteinemia that may increase with decreased dietary folate intake (39). Genetic defects in MTHFR lead to psychomotor growth delay, serious mental retardation, and other psychiatric problems in infancy (40).

One-third of psychiatric and psychogeriatric patients have low serum or erythrocyte folate levels (41,42). Folate deficiency affects normal brain development by different mechanisms (43). First, because folate is an essential precursor for DNA synthesis, deficiency disrupts the division of neural progenitor cells. Related to this, in a study of pregnant mice, it was found that folate deficiency disrupts the replication of progenitor cells in the ventricular germinal zones of the brain where a large proportion of cortical neurons begin to migrate (44). Second, folate deficiency may affect normal fetal brain development because of elevated homocysteine levels in the mother. During the third trimester of pregnancy, maternal hyperhomocysteinemia is associated with a 2-fold increased risk for schizophrenia in babies (45).

5.1. Psychosis (schizophrenia)

A relationship between methylation and schizophrenia was first established by Osmond and Smythies in 1952 (46). In that study, they hypothesized that methionine was a methyl donor for the synthesis of hallucinogenic amines. Further studies reported that folate deficiency was present in only 25%–30% of schizophrenics (47). However, in many studies, hyperhomocysteinemia has been the most common finding, especially in young and first-episode schizophrenia patients (48–50).

In addition, mean urine MMA levels may be significantly higher in patients with psychosis and depression. Thus, urine MMA measurements may provide more valuable information than serum vitamin B_{12}, and urine MMA measurements can show whether vitamin B_{12} has entered a cell (23). Another study showed that, in association with one-carbon metabolism, although erythrocyte membrane phosphatidylcholine concentrations were lower than in a control group, phosphatidylethanolamine concentrations were higher in schizophrenic patients because of impaired phospholipid methylation (51).

5.2. Alzheimer's disease

People who develop Alzheimer's disease may have had increased homocysteine levels earlier in life. Indeed, elevated homocysteine is often considered an early sign of cognitive impairment in geriatrics (52,53). There is also a strong association between low folate concentrations and cerebral cortex atrophy (54). In addition, although folate levels are 3- to 4-fold higher in cerebrospinal fluid (CSF) than in blood in healthy individuals, Alzheimer's disease patients have significantly low levels of CSF folate (55). In addition, SAM concentrations are lower in the CSF of Alzheimer's disease patients compared to healthy controls of the same mean age (56).

5.3. Autism

Approximately 20 years ago, health institutes recommended folic acid support for pregnant women to protect against neural tube defects (NTDs). Investigations have shown that after folate supplementation, NTD incidence decreases by approximately 70% and its clinical severity is also reduced (57). However, as folic acid fortification has increased, so has the incidence of autism, suggesting another problem. In the United States, it has been reported that the incidence of autism increased after folate fortification (58,59). The Autism Genome Project Consortium noted that the glutamatergic neural system and genes associated with glutamate may contribute to the appearance of autism spectrum disorders (60). Glutamate pathways play

key roles in the development of the neural system, and glutamatergic system disorders may cause autism (61). All folate species contain at least one glutamate residue and potentially facilitate the excitatory properties of glutamate (61): they inhibit high-affinity glial uptake of glutamate, compete with inhibitor neurotransmitters for binding to receptors, and slow glutamate decarboxylase activity. The kainic acid receptor is a subunit of glutamate receptor 6 and a mutation in the kainic acid receptor gene may be associated with autism (62).

6. Conclusion

In spite of intensive research into neuropsychiatric disorders, adequate explanations for their pathogenesis and biochemical diagnostic markers are not available yet. Psychiatric diagnosis is specifically based on the behavioral aspects. In these diseases, some evidence about disorders of the one-carbon cycle regulation or folate metabolism has begun to emerge. Although biomarkers of impaired one-carbon metabolism show relationships at the level of common findings in neuropsychiatric disorders, the evidence is insufficient to establish a causal relationship. However, once one-carbon metabolism dysregulation is restored, significant improvements in symptoms can be seen in these patients. Further investigations into the relationships between one-carbon metabolism and neuropsychiatric disorders could illuminate their pathogenesis.

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