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Why does hyperglycinemia exhibit so grave brain anomalies and so severe neurological symptoms?

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ABSTRACT

Nonketotic-hyperglycinemia (NKH) is an autosomal recessive disorder associated with grave brain malformations and severe neurological symptoms, and also characterized by accumulation of a large amount of glycine in body fluids. NKH is caused by an inherited deficiency of the glycine cleavage system (GCS), which is the main system to degrade glycine in mammalians. These severe symptoms and grave bran malformations are not normally observed in the other amino acid metabolic disorders, suggesting that GCS should have unknown pivotal roles in brain development and function. Interestingly, GCS is indispensable in supplying proliferating cells with 5,10-methylenetetrahydrofolate as a one-carbon donor, which is essential for the synthesis of DNA in cell proliferation. Since GCS is expressed intensely and ubiquitously in the neuroepithelium, the lack of GCS might greatly impair the proliferation of neural stem cells. On the other hand, this system is also very important to regulate extracellular glycine concentrations. Since glycine is an important neurotransmitter, which binds to both glycine receptors and NMDA receptors, high glycine concentrations caused by the deficiency of GCS might cause the aberrant neurotransmission in the patient brains. Considering these unique two faces of GCS functions, proliferation disturbance and aberrant neurotransmission are intricately mixed in the developing brain, leading to the grave brain malformations and sever neurological symptoms.

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1. Introduction

Nonketotic-hyperglycinemia (NKH), also known as glycine encephalopathy, is an autosomal recessive disorder associated with neonatal apnea and seizures, followed by severe psychomotor retardation in those who survive their ventilator-dependent period after birth (Hoover-Fong et al., 2004). NKH is caused by an inherited deficiency of the glycine cleavage system (GCS, also called glycine synthase; EC 2.1.2.10), which is the main system to degrade glycine in mammalians and this congenital metabolic disease is characterized by accumulation of a large amount of glycine in body fluids, particularly in cerebrospinal fluid (Tada et al., 1969; Hayasaka et al., 1987). Glycine is degraded by GCS into active C1 unit ("C_1"), which is used for 5,10-methylenetetrahydrofolate synthesis, and CO_2, NH_3 (Kikuchi, 1973; Fig. 1). In addition to the importance for glycine degradation, GCS is also necessary to supply 5,10-methylenetetrahydrofolate as a one-carbon donor, which is essential for the synthesis of DNA in cell proliferation (Fleming and Copp, 1998). Not only the patients develop sever neurological symptoms such as coma, respiratory distress and intractable seizures within the first few days of life, but also grave brain malformations, such as agenesis of the corpus callosum, gyral malformations and cerebellar hypoplasia are also frequently accompanied (Press et al., 1989; Dobyns, 1989; Nissenkorn et al., 2001). These severe symptoms and grave bran malformations are not normally observed in the other amino acid metabolic disorders, suggesting that GCS should have unknown pivotal roles in brain development and function. However, the relationship between the dysfunction of GCS and the occurrence of grave brain malformations and severe neurological symptoms is largely unknown. Thus, in this manuscript, I try to find the missing link between them.

2. Hypothesis

GCS in the CNS has various functions. First, GCS is indispensable in supplying proliferating cells with 5,10-methylenetetrahydrofolate as a one-carbon donor, which is essential for the synthesis of DNA in cell proliferation (Fleming and Copp, 1998). Interestingly, GCS is expressed intensely and ubiquitously in neural stem/progenitor cells in the neuroepithelium (Ichinohe et al., 2004). Therefore,

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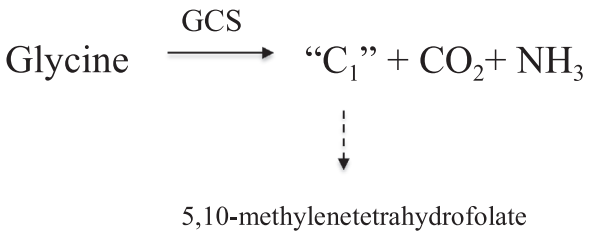

Fig. 1. The glycine cleavage system.
Glycine is degraded by the glycine cleavage system (GCS) into active C1 unit ("C_1"), which is used for 5,10-methylenetetrahydrofolate synthesis, and CO_2, NH_3.

the lack of GCS might greatly impair the proliferation of neural stem cells, leading to grave brain malformations and severe clinical symptoms. Second, this system is also very important to regulate extracellular glycine concentrations. Since glycine is an important neurotransmitter, which binds to both glycine receptors and NMDA receptors, extracellular glycine concentrations should be tightly regulated by the glycine cleavage system. Thus, high glycine concentrations caused by the deficiency of GCS might cause the aberrant neurotransmission in the patient brains, leading to grave brain malformations and sever neurological symptoms. Taken together, I speculate the following hypothesis.

Here, the hypothesis is as follows (Fig. 2);

(1) Deficiency of GCS causes the lack of 5′,10′-methylentetrahydrofloate in neuroepithelial cells.
(2) Lack of 5′,10′-methylentetrahydrofloate impairs DNA synthesis and results in the dysgenesis of the brain.
(3) Deficiency of GCS also induces high glycine concentrations in the extracellular space in the CNS.
(4) High concentrations of extracellular glycine overactivate glycine receptors and NMDA receptors.
(5) Taken together, grave brain malformations and severe clinical symptoms occur.

3. Evaluation of the hypothesis

3.1. Non-ketotic hyperglycinemia and the glycine cleavage system

NKH is a heritable disorder of amino acid metabolism caused by an inherited deficiency of GCS, in which large quantities of glycine accumulate in plasma, urine, and cerebrospinal fluid. Onset of the disease occurs most often in early infancy. Clinical manifestations include seizures, abnormal muscle tone and reflexes, and pronounced developmental delay, and grave brain anomalies (Tada et al., 1969; Hayasaka et al., 1987). GCS catalyses the direct cleavage of glycine to form active C1 unit ("C_1"), which is used for 5,10-methylenetetrahydrofolate synthesis, carbon dioxide and ammonia (Fig. 1). It consists of four proteins referred to as P-protein, H-protein, T-protein, and L-protein (Kikuchi, 1973). P-, T-, and H-proteins are encoded by GLDC, AMT, and GCSH genes, respectively. In patients with NKH, specific mutations have been identified in the GLDC gene (Kure et al., 1992), AMT gene (Nanao et al., 1994) and GCSH gene (Kure et al., 2002), providing unequivocal evidence that deficiency of the GCS causes NKH. This system is considered to be a major pathway for the catabolism of glycine in vertebrates, including mammals, birds, reptiles, amphibians and fishes (Kikuchi, 1973; Yoshida and Kikuchi, 1973). GCS in animals is biochemically confined to the mitochondria, as an enzyme complex that is loosely bound to the inner mitochondrial membrane (Hiraga et al., 1972; Motokawa and Kikuchi, 1971).

3.2. GCS in brain development

Brain is derived from the neural tube, comprised of neuroepithelial cells. Neuroepithelial cells are the stem cells of the nervous system, and differentiate into multiple types of cells, like neurons, astrocytes and other glial cells. Interestingly, GCS is expressed intensely and ubiquitously in neural stem/progenitor cells in the neuroepithelium (Ichinohe et al., 2004). As mentioned above, GCS is indispensable in supplying proliferating cells with 5,10-methylenetetrahydrofolate as a one-carbon donor, which is es-

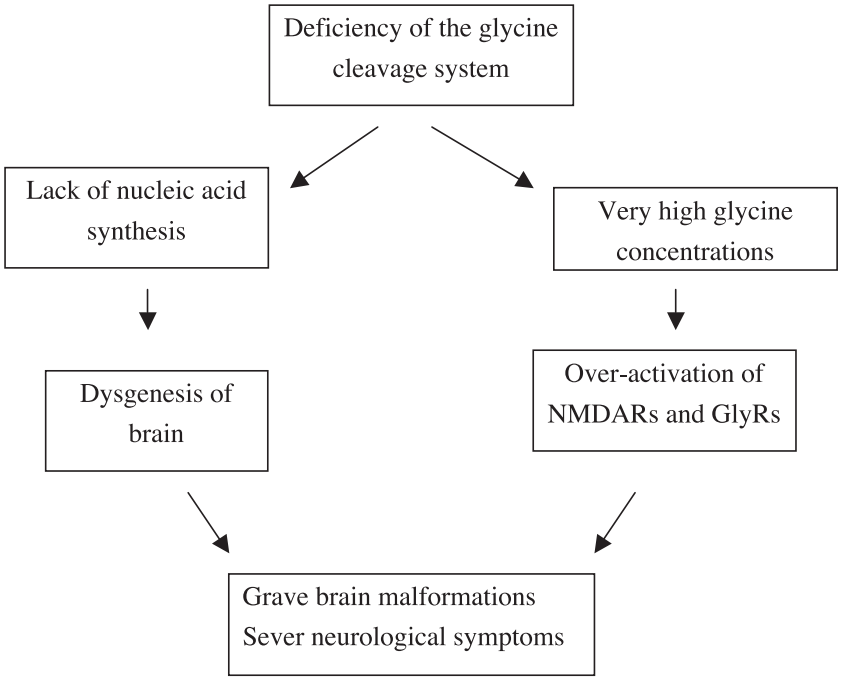

Fig. 2. Basic concept.

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