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Possible mechanisms of homocysteine in the pathogenesis of depressive disorder

Subinuli Asimujian[1], Yi Zhang[2*]

[1]Xinjiang Medical University, Urumqi, China
[2]The People's Hospital of Xinjiang Uygur Autonomous Region, Urumqi, China

*Corresponding Author. Email: 515337975@qq.com

Abstract. Depressive disorder is one of the mental illnesses with the highest global disability rates. Homocysteine (Hcy), a non-essential sulfur-containing amino acid, serves as a significant risk factor in the development and progression of various diseases. Current research has revealed a close association between Hcy and depressive disorder. This review focuses on elucidating the mechanisms of Hcy in the pathogenesis of depressive disorder and explores its potential as both a biomarker and a therapeutic target.

Keywords: depression, homocysteine, hyperhomocysteinemia, pathogenesis

1. Introduction

Depressive disorder is a common mental disorder, caused by a variety of reasons to significant and persistent depressive symptoms as the main clinical features of a class of mood disorders, the core symptoms are disproportionate to the situation of sad mood, loss of interest and energy fatigue, with a high incidence rate, high relapse rate, high self-harm rate of clinical features, seriously affecting the patient's psychosocial functioning, and aggravate the global burden of disease. According to World Health Organization (WHO) statistics, approximately 3.8% of the global population is affected by depressive disorders, with prevalence in women being 1.5-2 times higher than in men [1]. The International Consortium for Psychiatric Epidemiology conducted investigations using the WHO Composite International Diagnostic Interview among 37,000 participants across 10 countries including the United States, European nations, Asian countries, and found that the lifetime prevalence of depressive disorders ranged from 8% to 12% in most countries, with the United States having a prevalence rate of 16.9%. A 2021 cross-sectional study in China demonstrated an overall prevalence rate of 3.6% for depressive disorders [2]. According to WHO, depressive disorders have risen to the second place in the burden of disease ranking in China and are expected to be the first in the global burden of disease in 2030 [3]. Recent studies have identified a close correlation between Homocysteine (Hcy) levels and the development of depressive disorders.

Hcy is a non-essential α-amino acid and an intermediate product generated during methionine metabolism in the body. Approximately 98% of Hcy in the body exists in an oxidized form. The fasting physiological serum Hcy level ranges from 5~15 μmol/L. Hcy does not directly participate in protein synthesis and is rarely obtained from dietary sources, primarily originating from ingested methionine, which is found in foods such as cheese, eggs, nuts, and meat. Hcy metabolism involves two pathways: the transculturation pathway and the remethylating pathway. Folic acid, vitamin B6, and vitamin B12 act as critical cofactors in Hcy metabolism, facilitating these processes and helping maintain the dynamic balance of Hcy levels.

2. Hyperhomocysteinemia and risk factors

When Hcy metabolism is disrupted, leading to elevated Hcy levels in the body, a serum Hcy concentration exceeding >15 μmol/L results in HyperHomocysteinemia (HHcy). HHcy is classified into mild (15-30 μmol/L), moderate (30-100 μmol/L), and severe (over 100 μmol/L) categories [4]. In recent years, the incidence of HHcy has shown an increasing trend. A meta-analysis in 2021 reported that the incidence of HHcy in China is approximately 37.2%, which is significantly higher than the 27.5% incidence reported in 2012 [5]. Research results indicate that HHcy is closely associated with the occurrence and development of various diseases, such as cardiovascular diseases, stroke, chronic renal failure, megaloblastic anemia, osteoporosis, venous thrombosis,

inflammatory bowel disease, and cognitive impairment. For every 5 μmol/L increase in plasma Hcy levels, the risk of all-cause mortality rises by 33.6%, and the risk of depressive disorders increases by 26%. Hcy levels are influenced by numerous factors, including genetics, enzyme dysfunction, cofactor deficiencies, excessive methionine intake, age and gender, specific diseases such as chronic kidney failure, hypothyroidism, and anemia, the use of certain medications such as cholinergic agents, methotrexate, oral contraceptives, phenytoin, carbamazepine, or metformin, and lifestyle habits [6].

3. Depressive disorder and hcy

The etiology and pathogenesis of depressive disorders are multifactorial and complex, and have not yet been fully elucidated, it is related to genetic factors, neurobiochemical, neuroendocrine, and psychosocial factors.In recent years, the role of metabolic abnormalities, especially the dysregulation of one-carbon metabolism, in the development of depressive disorders has attracted the attention of many scholars. Hcy as a key metabolic biomarker, has been demonstrated to closely correlate with the pathological mechanisms of depressive disorders. recent study showed a relatively strong correlation between depressive disorders and HHcy [7]. In a study by Phillip et al., after adjusting for variables such as age, sex, physical activity, and education, elevated Hcy levels were found to a positive correlation with depressive symptoms [8]. Another prospective study found that increased Hcy concentrations at both baseline and after follow-up were associated with depression at 2 years [9].A 2020 meta-analysis on major depressive disorder mentioned that folate supplementation improved symptoms in refractory major depressive disorder, especially in patients with depressive disorder resistant to Selective Serotonin Reuptake Inhibitors (SSRIs) and those exhibiting biomarkers related to inflammation, metabolic disorders, or genetic polymorphisms in folate metabolism have the best response [10]. Kwok et al. conducted a randomized controlled trial in which 279 patients with mild cognitive impairment aged 65 years and older were randomized into experimental and control groups and supplemented with methylcobalamin and folic acid for 24 months. Follow-up found that compared to the placebo control group, the experimental group exhibited significantly reduced plasma Hcy concentrations and marked improvement in depressive symptoms at the 12-month [11].

4. Pathogenesis

HHcy interferes with normal neuronal function through multiple mechanisms, including DNA damage, disruption of neurotransmitters, oxidative stress, neuroinflammation, neurotoxicity, and aberrations in genetic and epigenetic regulation, thereby inducing the development of depression.

4.1. Neurotransmitter synthesis disorders

Serum Hcy is a monoamine neurotransmitter precursor, serves as a substrate for the synthesis of neurotransmitters such as norepinephrine, dopamine, and serotonin. Dysregulated Hcy metabolism interfere with monoamine neurotransmitters, thereby increasing the risk of depressive disorders. Serum Hcy mediates methionine metabolism and indirectly inhibits the synthesis and release of neurotransmitters such as norepinephrine, dopamine and 5-hydroxytryptophan, which not only play a key role in the pathogenesis of depressive disorders, but also serve as an important target for antidepressant drug therapy. S-Adenosylmethionine (SAM) is produced during the Hcy metabolism, not only had antidepressant properties but also acts as a methyl donor involved in methylation processes of monoamine neurotransmitters within the central nervous system. depression Patients with elevated plasma Hcy concentrations demonstrate reduced serum and erythrocyte folate levels, as well as decreased cerebrospinal fluid SAM concentrations [12]. Clinical studies found that SAM is an effective adjunctive therapeutic agent for patients with SSRI-resistant Major Depressive Disorder (MDD) [13].

4.2. Neurotoxic effects

Hcy exhibits neurotoxicity, broadly impair neuronal activity and affect the production and release of neurotransmitters. Previous animal experiments have found that mice injected intraperitoneally with Hcy had elevated Hcy concentrations in the striatal region and were found to have reduced motor function, suggesting that excess Hcy caused damage to dopaminergic neurons [14]. Another study found that Hcy-treated stroke rats showed a reduction in the number of synaptic and postsynaptic dense areas of neuronal cells and increased depression-like symptoms [15]. Excessive Hcy induces neurotoxicity through its dual effects on N-Methyl-D-Aspartate (NMDA) receptors, which contain binding sites for glutamate (an excitatory neurotransmitter) and glycine (an inhibitory neurotransmitter). Hcy is an agonist at the glutamate-binding site of NMDA receptors and a partial antagonist at the glycine-binding site. Consequently, HHcy triggers excessive activation of glutamate NMDA receptors, enhancing glutamate binding while diminishing glutamate uptake by nerve terminals. This results in elevated glutamate concentrations in the synaptic cleft, leading to excitotoxic neuronal death [16].

4.3. Oxidative stress and mitochondrial damage

Oxidative stress, a detrimental process caused by excessive free radical generation in the body, is recognized as a critical contributor to aging and disease. The sulfhydryl group of Hcy is prone to auto-oxidation, generating Reactive Oxygen Species (ROS) that induce lipid peroxidation and neuronal cell damage [17]. Excess Hcy exacerbates vascular oxidative burden by activating Nitric Oxide Synthase (NOS), promoting superoxide radical production. Additionally, Hcy metabolism involving protein-related pathways generates Hcy-Thiolactone (HTL), N-Hcy-protein, and N-epsilon-homocysteinyl-lysine, which produce ROS and lead to protein damage and structural alterations [18]. Hcy activates Inducible Nitric Oxide Synthase (iNOS) while suppressing endothelial Nitric Oxide Synthase (eNOS), resulting in increased peroxynitrite ($ONOO^-$) formation and subsequent neurocellular oxidative stress. Furthermore, Hcy inhibits the expression or reduces the activity of antioxidant enzymes, exacerbating systemic oxidative stress.

Hcy-induced apoptosis is closely linked to increased mitochondrial membrane permeability and diminished mitochondrial membrane potential. Hcy promotes neuronal calcium influx, amplifies mitochondrial oxidative stress, and inhibits DNA methylation, thereby accelerating neuronal apoptosis. Studies have shown that elevated Hcy levels in animal brains correlate with suppressed mitochondrial electron transport chain activity, reduced respiratory enzyme complex (II–V) function, elevated mitochondrial membrane potential, and increased ROS production. Hcy upregulates mitochondrial fusion-related proteins and autophagy markers such as LC3-II in murine cerebrovascular endothelial cells, suggesting its role in impairing mitochondrial function and modulating autophagy in the central nervous system [19]. Research indicates that ROS generated via Hcy-induced oxidative stress pathways damage cerebrovascular endothelial cells and promote atherosclerosis, further compromising the Blood-Brain Barrier (BBB). These processes drive neuroinflammation and contribute to the development and progression of depressive disorders.

4.4. Activation of neuroinflammation

Neuroinflammation is a pivotal hypothesis in the pathological mechanisms of depressive disorders, and Hcy plays a role in initiating and exacerbating cerebral neuroinflammatory processes. A study demonstrated a positive correlation between serum Hcy levels and peripheral High-Sensitivity C-Reactive Protein (hs-CRP) in patients with depressive disorders [20]. Hcy also induces activation of Nuclear Factor Kappa-B (NF-κB) in murine brains, increasing the release of pro-inflammatory cytokines such as Interleukin-1β (IL-1β), Tumor Necrosis Factor-Alpha (TNF-α), and other inflammatory mediators, thereby amplifying neuroinflammatory responses in brain tissues [21]. Excessive Hcy stimulates Vascular Smooth Muscle Cells (VSMCs) to produce CRP at both mRNA and protein levels, triggering immune activation and inflammation that drive excessive ROS release. This oxidative stress cascade activates NF-κB in vascular endothelial cells, macrophages, and VSMCs, while endothelial dysfunction disrupts the expression of neurotrophic factors such as Brain-Derived Neurotrophic Factor (BDNF) [20]. Additionally, Hcy increases Blood-Brain Barrier (BBB) permeability, facilitating the entry of peripheral inflammatory factors into the central nervous system. This activates microglia and initiates neuroinflammation within the central nervous system [22].

4.5. Epigenetic dysregulation

The intermediate metabolite of Hcy metabolism, S-Adenosylhomocysteine (SAH), inhibits DNA Methyltransferases (DNMTs), leading to genome-wide hypomethylation. Additionally, studies suggest that Bax (pro-apoptotic) and Bcl-2 (anti-apoptotic) proteins, critical regulators of cell survival or death following apoptotic signaling, may contribute to the pathogenesis of depression. Elevated Hcy levels increase Bax protein expression, which modulates cytochrome c release and propagates the apoptotic cascade through interactions with Bcl-2. This process induces ROS generation, alters DNA and protein expression, and ultimately drives cellular apoptosis or aberrant signaling [23].

5. Conclusion

Research evidence suggests a strong association between Hcy and depressive disorders. Excess Hcy levels have potential neurotoxic effects, especially on dopaminergic neurons that cause depressive disorders. The prevention and treatment of depressive disorders remain a major focus and challenge in psychiatric research. Elucidating the neurotoxic mechanisms of HHcy and its role in the pathophysiological processes of depressive disorders will advance the development of targeted therapeutic and preventive strategies. Future studies are warranted to validate the Hcy-depression relationship, further explore the causal relationship, and delineate underlying mechanisms, thereby providing novel insights and approaches for the prevention, diagnosis, and treatment of depressive disorders.

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