Hyperhomocysteinemia in Ischemic Brain Damage

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Technology description

A rodent model of hyperhomocysteinemia and using this model, they have demonstrated that predisposition to even mild hyperhomocysteinemic conditions drastically aggravates ischemic brain damage.
Using a pharmacological inhibitor targeting a specific N-methyl-D-aspartate receptor subunit (GluN2A subunit of NMDAR), the study demonstrated that inhibition of this specific NMDAR subunit significantly reduces ischemia-induced brain damage in both rats and mice predisposed to hyperhomocysteinemia, but has no effect in rodents with normal levels of homocysteine.
Complementary studies in GluN2A knockout mice show that in the absence of GluN2A-subunit of NMDAR, hyperhomocysteinemia-associated exacerbation of ischemic brain injury is blocked. This later finding validates the role of GluN2A-NMDAR as a critical determinant of the severity of ischemic brain damage under hyperhomocysteinemic conditions. Taken together, the findings show that hyperhomocysteinemia triggers unique signaling pathways that in conjunction with ischemia-induced pathways enhance the pathology of stroke under hyperhomocysteinemic conditions.

Background

Hyperhomocysteinemia is a common metabolic disorder characterized by systemic elevation of the thiol amino acid, homocysteine. Epidemiological studies have linked mild to moderate increases in plasma homocysteine levels (15-100 μM) to nutritional deficiency of folate, vitamin B12 and vitamin B6, and are considered to be risk factors for both acute and chronic neurological disorders. To reduce homocysteine related disorders in the USA, the FDA mandated fortification of food with folic acid (Federal Register 61:8752, 1996). In spite of this preventive measure the incidence of hyperhomocysteinemia in the elderly population is significantly large. This is mainly due to age-dependent low nutritional absorption, decreased metabolic function with advanced age, insufficient renal or hepatic function and side effect of medications. Depending on gender differences, 44-46% of the elderly population (60 years and older) is found to be hyperhomocysteinemic in the USA. The prevalence of hyperhomocysteinemia outside the USA is even higher (66–76%).
According to the National Institute of Health (NIH), numerous epidemiological reports have established hyperhomocysteinemia as an independent risk factor for cardiovascular disease, cerebrovascular disease, dementia-type disorders, and osteoporosis-associated fractures. Although combined folic acid and B-vitamin therapy substantially reduces homocysteine levels, results from randomized placebo-

controlled clinical trials testing the effect of vitamin therapy on outcome in these diseases are mixed, but have generally fallen short of expectations. As a result, further research and development regarding treatment of neurological disorders in individuals predisposed to hyperhomocysteinemia are needed.

Technology Description

The incidence of cerebral ischemic stroke, the fourth largest cause of death and a leading cause of disability in USA, is most prevalent in the elderly population. Researchers at the University of New Mexico have developed a rodent model of hyperhomocysteinemia and using this model, they have demonstrated that predisposition to even mild hyperhomocysteinemic conditions drastically aggravates ischemic brain damage. They have further established that cerebral ischemic stroke under hyperhomocysteinemic conditions triggers two divergent pathogenic pathways resulting in the exacerbation of ischemic brain injury. Using a pharmacological inhibitor targeting a specific N-methyl-D-aspartate receptor subunit (GluN2A subunit of NMDAR), the study demonstrated that inhibition of this specific NMDAR subunit significantly reduces ischemia-induced brain damage in both rats and mice predisposed to hyperhomocysteinemia, but has no effect in rodents with normal levels of homocysteine. Complementary studies in GluN2A knockout mice show that in the absence of GluN2A-subunit of NMDAR, hyperhomocysteinemia-associated exacerbation of ischemic brain injury is blocked. This later finding validates the role of GluN2A-NMDAR as a critical determinant of the severity of ischemic brain damage under hyperhomocysteinemic conditions. Taken together, the findings show that hyperhomocysteinemia triggers unique signaling pathways that in conjunction with ischemia-induced pathways enhance the pathology of stroke under hyperhomocysteinemic conditions. This novel finding could result in the development of potential therapeutic targets for treatment of cerebral ischemic stroke and related disorders in individuals predisposed to hyperhomocysteinemia.

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Application area

Establishes that ischemic insult under hyperhomocysteinemic condition exacerbates ischemic brain injury and functional deficits.
Highlights the role of GluN2A-NMDAR in neurodegeneration resulting from cerebral stroke.
Establishes the therapeutic potential of GluN2A-NMDAR antagonists in reducing ischemia induced brain damage and functional deficit.

Institution

The University of New Mexico

Inventors

Surojit Paul
Ranjana Poddar

联系我们

叶先生

电 话：021-65679356

手 机：13414935137

邮 箱：yeyingsheng@zf-ym.com