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Review article

Homocysteine and schizophrenia: From prenatal to adult life

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Abstract

Homocysteine is becoming increasingly recognized as an important substance in the pathogenesis and pathophysiology of schizophrenia. In this review, we first present background information supporting a role for homocysteine in schizophrenia. We then discuss our work on the role of hyperhomocystinemia during adulthood and risk of schizophrenia, and present preliminary evidence on a potential relationship between prenatal homocysteine and schizophrenia. Finally, we discuss the implications of these findings for future work on nutritional etiologies of schizophrenia.

Keywords: Homocysteine; Schizophrenia

Contents

1. Introduction

Increasing evidence supports a role for an elevation of homocysteine in schizophrenia. In this paper, we shall review our work on studies of homocysteine abnormalities in adult patients with schizophrenia, and our preliminary research findings on elevated homocysteine during pregnancy and risk of schizophrenia in the offspring. This work has the potential to increase our understanding of the biochemical mechanisms that underlie the pathophysiology of schizophrenia and yield new approaches to prevention of this disorder.

Abbreviations: CNS, central nervous system; HPLC, high performance liquid chromatography; ICD, International Classification of Diseases; KPMCP, Kaiser Permanente Medical Care Plan; MTHFR, methylenetetrahydrofolate reductase; NMDA, *N*-methyl-D-aspartate; NTD, neural tube defects; PDS, Prenatal Determinants of Schizophrenia Study.

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2. Dutch famine study

Our interest in homocysteine originated from our studies of schizophrenia after prenatal exposure to the Dutch Hunger Winter of 1944–1945 (Susser et al., 1996; Susser and Lin, 1992). This tragic event in human history also presented a unique opportunity: to examine the role of prenatal nutrition in the etiology of schizophrenia. The famine was precipitated by a Nazi blockade in the last year of World War II. The famine commenced in October 1944 and gradually worsened over the subsequent months, until liberation in early May, 1945. The famine reached its peak between February and April, 1945. High mortality, low fertility, and increased adverse birth outcomes were observed (Stein et al., 1975). The cities of the western Netherlands were most affected.

Several features of the famine and the situation in Holland contributed to the research design advantages of the study. The famine was brief and well-circumscribed, food rations were well-documented, and the Netherlands maintained a comprehensive database on psychiatric outcomes. Using these data, we found that individuals who were exposed to the famine during the periconceptional period, but not at other times in pregnancy, had a twofold and significantly increased risk of adult schizophrenia. An increased risk of congenital central nervous system (CNS) defects, mostly neural tube defects (NTDs), were also observed in individuals who were exposed to the famine during this period of gestation.

We considered several nutritional, and non-nutritional, factors that might explain this finding. These are discussed in previous publications (Brown et al., 1996; Susser et al., 1996). One potential candidate nutrient is folic acid, given that folic acid supplementation during the periconceptional period has been well-documented to prevent neural tube defects (MRC Vitamin Study Research Group, 1991). Additional studies have shown diminished red blood cell (Kirke et al., 1993; Smithells et al., 1976; Yates et al., 1987) and serum folate levels (Kirke et al., 1993) in pregnant mothers who later gave birth to offspring with neural tube defects.

3. Schizophrenia and impaired homocysteine metabolism

It has been demonstrated in previous studies that neural tube defects are related to a genetic defect in homocysteine metabolism (Van der Put et al., 1995; Whitehead et al., 1995). Sufficient intake of folic acid is believed to reduce this risk by enhancing methylation of homocysteine and its conversion to methionine, thereby compensating for this genetic defect. It has been shown that plasma homocysteine levels are elevated when folate levels were in the lower half of the normal range (Jacques et al., 1996). These studies, and our previous work on the Dutch famine study, led us to consider the hypothesis that patients with schizophrenia might have a genetic defect in homocysteine metabolism which would be overcome by high folate intake. This hypothesis would predict that schizophrenia cases with low folate would have increased homocysteine levels, compared to controls, since dietary folate would be insufficient to compensate for the genetic defect. Although previous investigations of schizophrenia have demonstrated increased homocysteine levels compared to controls, it has not yet been documented whether these increases were specific to a subgroup with low folate levels.

3.1. Case-control study of homocysteine and adult schizophrenia

We therefore conducted a case-control study that aimed to compare homocysteine levels between cases and controls, stratified by serum folate level (Susser et al., 1998). The patients consisted of 30 subjects with schizophrenia or schizoaffective disorder (DSM-III-R) (American Psychiatric Association, 1987), who resided on our Schizophrenia Research Unit of Columbia University; the controls were 33 volunteers who were recruited from the community, and in whom psychiatric disorders had been ruled out by a standardized diagnostic interview. The assay for homocysteine was by capillary gas chromatography–mass spectrometry (Allen et al., 1993). We quantified folate and cobalamin (vitamin B_{12}), the latter of which is a co-factor in the conversion of homocysteine to methionine, by standard radioimmunoassays.

We divided the subjects into two groups: those with low folate, defined as the bottom tertile for controls, and all others. The low-folate group consisted of 6 cases and 8 controls; the non-low-folate group consisted of 11 cases and 16 controls.

We found that the mean homocysteine level in cases among the low folate group was 10.7 μM (S.D.=3.2) and the mean homocysteine level in the controls among the low folate group was 7.7 μM (S.D.=1.4) ($t=2.4$, $df=12$, $p=0.03$). We also examined the data using a dichotomous measure of homocysteine (defined as >90th percentile for controls). Under this definition, 4 cases among the low folate group, and no controls among the low folate group had elevated homocysteine (Fisher's $p=0.01$, two-tailed). Cobalamin levels were similar between cases and controls. In contrast, there were no differences in mean homocysteine levels among the low folate group.

These data support the hypothesis that a subtle genetic defect in homocysteine metabolism may play an etiologic role in schizophrenia. Consistent with our finding, several studies have demonstrated that a polymorphism in the gene for methylenetetrahydrofolate reductase (MTHFR) is associated with schizophrenia (Arinami et al., 1997; Joober et al., 2000). MTHFR catalyzes the conversion of methylenetetrahydrofolate to methyl tetrahydrofolate. This process yields a methyl group which is donated to homocysteine in its conversion to methionine. Thus, a deficiency of MTHFR is associated with elevated homo-